The New England
Journal of Medicine

Copyright, 1954, by the Massachusetts Medical Society

Volume 251 DECEMBER 30, 1954 Number 27

ADENOIDAL-PHARYNGEAL-CONJUNCTIVAL AGENTS*

A Newly Recognized Group of Common Viruses of the Respiratory System

ROBERT J. HUEBNER, M.D.,† WALLACE P. ROWE, M.D.,‡ THOMAS G. WARD, M.D.,§
ROBERT H. PARROTT, M.D.,¶ AND JOSEPH A. BELL, M.D.‖

BETHESDA, MARYLAND

THE undifferentiated respiratory diseases, the febrile catarrhs (acute respiratory disease, exudative nonstreptococcal pharyngitis, primary atypical pneumonias)[1,2] and the afebrile common colds continue as unsolved omnipresent sources of human distress. About two years ago our group at the National Microbiological Institute and a group at Johns Hopkins University School of Hygiene embarked on collaborative efforts to study these ailments. The general, quite elastic plan was to observe them in a concerted manner — to study them simultaneously from clinical, epidemiologic and laboratory standpoints. A particularly important and specific part of the plan, however, was to utilize tissue-culture technics providing multi-purpose new tools in efforts to demonstrate as yet unknown viruses from the respiratory tract that might have some relation to these illnesses.

We assumed, with the use of suitable tissue-culture systems, that newly recognized viruses would become available — not a very large assumption in view of the staggering number of still unclassified human viruses isolated by newly developed technics during the past several years. This backdoor approach, — that is, the attempt to find a disease to fit new viruses by observing their activity in the human community, — we believe, has much to recommend it. Technical problems of working with new viruses in the laboratory can frequently be worked out by the time opportunities become available for clinical and epidemiologic studies of their host-parasite behavior, permitting more precise construction of the entities produced than might otherwise be possible. This would seem an especially worthwhile procedure to apply in attempts to segregate specific etiologic entities from the "hotchpotch" described by Andrewes[3] that make up the undifferentiated respiratory diseases.

In a previous communication we reported 13 isolations of a new agent demonstrated in surgically removed human adenoids by growing of adenoidal epithelium in roller-tube tissue cultures.[4] Shortly thereafter we found that similar agents could be demonstrated by this technic in the tonsils and adenoids of a majority of persons undergoing surgical removal of these tissues. Subsequently, by using tissue cultures of human embryonic epithelium and HeLa cells, we demonstrated more than 100 strains of viruses, biologically and serologically related to the adenoid-tonsil agents, in nasopharyngeal and conjunctival secretions and feces of patients with undifferentiated respiratory diseases.[5]

Because our previous term, "adenoid-degenerating" agent is obviously inadequate, we are proposing the term "adenoidal-pharyngeal-conjunctival" agents as the generic designation for this new group of viruses. The new agents reported by Hilleman and Werner[6] in patients with acute respiratory illnesses and by Neva and Enders[7] in a patient with an illness resembling roseola infantum apparently belong in this group.

Our purpose in this paper is to present in general terms our findings, which are given in greater detail in reports now in press or in preparation.[4,8,8-10]

PROPERTIES

None of the agents, whose properties are shown in Table 1, produced unequivocal illness in any of the many laboratory animals tested.

The viruses were epitheliotropic, growing and causing changes in human epithelial cells more rapidly than in fibroblasts, even when both types of cell were present in the same culture tube. The changes occurred first in the peripheral cells of the

*From the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute, and the Department of Microbiology, School of Hygiene and Public Health, Johns Hopkins University.
Supported in part by grant from the Division of Research Grants, United States Public Health Service.

†Medical director, United States Public Health Service; chief, Virus and Rickettsial Diseases Section, Laboratory of Infectious Diseases, National Microbiological Institute; assistant professor of infectious diseases in pediatrics, Georgetown University School of Medicine.
‡Senior assistant surgeon, United States Public Health Service, Laboratory of Infectious Diseases, National Microbiological Institute.
§Associate professor of microbiology, Johns Hopkins University School of Medicine.
¶Senior assistant surgeon, Laboratory of Clinical Investigation, Clinical Center, National Microbiological Institute, National Institutes of Health; assistant clinical professor of pediatrics, Georgetown University, School of Medicine.
‖Medical director, United States Public Health Service; chief, Epidemiology Section, National Microbiological Institute, Laboratory of Infectious Diseases.

epithelial sheets; the cells became enlarged and rounded, and the external membranes refractile; the outer cytoplasm was clear, but the nuclei became indistinguishable in the large, granular, central portion of the cells. The cells then became pyknotic and fell from the wall of the tube. Seven to fourteen days were required for dissolution of large epithelial sheets. Involvement of fibroblasts was generally not noted until all epithelium was destroyed. The changes progressed slowly, often requiring several months for complete destruction of all fibroblastic cells.[5]

HeLa-cell tissue cultures* provided an excellent substrate for the growth of the agents, responding with characteristic cytopathogenic and metabolic effects that appeared quite different from the usual effects produced in the same tissue by other viruses such as those of poliomyelitis, herpes and vaccinia. Densely granular, rounded cells tightly clumped or fused together were seen twenty-four to seventy-two hours after inoculation with potent suspensions of adenoidal-pharyngeal-conjunctival viruses. The cell sheets were frequently completely dislodged from the walls of the tube within forty-eight hours of inoculation. At this time the culture fluids of infected tissues generally appeared much more acid than that of tissue controls — so that the effects of virus activity were frequently recognized by the strong yellow color given by the phenol-red indicator system in the media. Epithelial cells from monkeys and rabbits responded with cytopathogenic effects similar to those in human epithelium, particularly on primary passage. The viruses multiplied with considerable reluctance in such tissues. However, some evidence of greater adaptation was seen on serial passages.

TABLE 1. *Some Properties of Adenoidal-Pharyngeal-Conjunctival Viruses.*

1.	Production of unique cytopathogenic changes in:
	— human explant cultures (epitheliotropic)
	— HeLa cells, with acid production
	— monkey kidney
	— rabbit trachea
2.	Apathogenic for laboratory animals
3.	Ether resistant
4.	Heat labile (56°C. for 30 min.)
5.	Filtrable (sintered glass, Mandler)
6.	Resistant to antibiotics
7.	Type-specific neutralization
8.	Group-reactive complement-fixing antigens and antibodies (not type specific)
9.	Soluble antigen

The viruses were resistant to ether, a matter of importance in attempts to isolate viruses from contaminated natural sources — being most useful in the elimination of molds. They were passed with little or no loss in titer through various standard bacteria-tight filters. They proved completely resistant to sulfonamides and to currently available antibiotics such as penicillin, streptomycin, chlortetracycline and oxytetracycline but showed no unusual resistance to heat, being inactivated at 56°C. for thirty minutes.

*Supplied by Microbiological Associates, Incorporated, Bethesda, Maryland.

A complement-fixing antigen reported previously[6] with a soluble component was produced in comparatively large amounts in fluids from all types of infected cells. Large-bottle (1-liter prescription size) cultures of HeLa cells frequently yielded 20 to 40 cc. of fluid with virus titers as high as 10^{-6} and antigen titers of 1:32 when tested with 2 to 4 units of antibody in the presence of 2 full units of complement, the Bengtson C.F. technic modified by means of an overnight fixation period being used. All strains studied produced comparable amounts of antigen, which in large part was separable from the infectious particle by differential centrifugation. The antigen appears to be common to all types of adenoidal-pharyngeal-conjunctival viruses and represents an important property to be examined in characterizing the group.[5]

Immunologic Classification

The existence of different immunologic types of adenoidal-pharyngeal-conjunctival viruses became apparent early in our studies when serums from young infants neutralized some strains but not others. Similarly, antiserums prepared in rabbits and antibodies produced in human volunteers inoculated with certain strains neutralized homologous strains but not others. Crossneutralization with rabbit antiserums prepared against various strains has led to the construction of different immunologic classes (Table 2). These data show that reciprocal crossneutralizations occurred between some strains but not others, thus providing a basis for the establishment of serotypes. After 3 serotypes had been defined, Strain RI-67 was received from Dr. Maurice R. Hilleman. Since it satisfied all important criteria for inclusion in the group, sharing all the properties listed in Table 1, it was designated as the prototype of Type 4. Strains serologically identical with Type 4 were characterized a short time later, as well as strains requiring the creation of 2 additional serotypes. There seems to be little question that more serotypes will be encountered in the near future. A cytopathogenic agent recently reported by Neva and Enders[7] was found immunologically identical with Type 3. We have placed 143 of 171 separate strains isolated in this laboratory in 6 immunologic types.

The methods used in typing are described elsewhere.[5] However, it is important to mention that sensitivity and specificity were much influenced by variations in the procedures used in neutralization and that tests of greater sensitivity revealed certain amounts of crossreactions between types not shown in Table 2. Another factor of importance in strain typing is variable minor heterotypic responses, which occur in both human beings and rabbits.[5] The criteria selected for determining serotypes and the inclusion of new strains within a certain serotype are therefore of obvious importance, since simple, one-directional reactions could lead to erroneous typing of strains.

In these early stages of this study we believe that construction of serotypes within the adenoidal-pharyngeal-conjunctival group based on reciprocal crossneutralizations by rabbit antiserums requires the supporting evidence furnished by human infections with the proposed serotypes. Table 3 shows the neutralizing antibody responses of 6 persons, each known to have been infected by a representative of each of the types. In almost all cases the antibody responses of infected persons show a fourfold, or greater, rise against the serotype recovered from them and in general no response, or much lesser responses, to heterotypes.

TABLE 2. *Neutralization by Rabbit Antiserums.**

Immunizing Virus	Type 1 Virus			Type 2 Virus		Type 3 Virus		Type 4 Virus		Type 5 Virus		Type 6 Virus
	Ad. 1	Ad. 71	Ad. 63	Ad. 6	Ad. 84	G.B.	J.H.	RI 67	R.N.	Ad. 75	Ton. 80	Ton. 99
Ad. 1	+	+	+	−	−	−	−	−	−	−	−	−
Ad. 63		+		−		−		−				
Ad. 6	−	−	−	+	+	−	−	−		−		
Ad. 84	−	−		+	+	−		−	−		−	−
G. B.		−	−	−	−	+	+	−	−	−	−	−
J. H.	−			−		+	+					
RI 67		−		−		−		+	+	−		−
R. N.		−		−		−		+	+	−		−
Ad. 75		−		−		−		−		+	+	−
Ton. 80		−		−		−		−		+	+	−
Ton. 99		−		−		±		−		−	−	+

*+ = neutralization.

TABLE 3. *Antibody Responses of Human Patients Infected with 6 Adenoidal-Pharyngeal-Conjunctival Viruses.*

Infecting Virus Type	Neutralizing Antibody Titer						Complement-Fixing Antibody Titer					
	Type 1	Type 2	Type 3	Type 4	Type 5	Type 6	Type 1	Type 2	Type 3	Type 4	Type 5	Type 6
1*	< 4 64	>64 >64	< 4 < 4	4 4	< 4 < 4	< 4, > 4,<16	< 8 > 64	< 8 > 64	< 8 64	< 8 < 8	< 8 32	< 8 64
2*	< 4 > 4,<16	< 4 64	4 4	4 16	16 16	4 16	< 8 > 64	< 8 128	< 8 64	< 8 > 64	8 > 64	32 > 64
3†	>64 >64	4 > 4,<16	< 4 >16	> 4,<16 > 4,<16	4 16	< 4 4	64 > 64	32 > 64	< 8 > 64	< 8 > 64		
4†	< 4 < 4	< 4 < 4	< 4 4	< 4 64	< 4 < 4	< 4 < 4	< 8 64	< 8 32	< 8 64	< 8 64		
5*	<16 >16,<64	>64 >64	16 16	16 16	< 16 >256	16 64	< 8 128	< 8 128	8 128	< 8 128	< 8 >128	< 8 256
6*	16 16	< 4 16	> 4,<16 > 4,<16	16 16	> 64 > 64	4 16	16 1024	16 1024	8 >1024	32 1024	32 512	< 8 512

*Volunteer infected with indicated type.
†Natural infection with indicated type.

Except for Types 5 and 6, of which only one human infection each has been studied in the neutralization tests, we have data on at least several per-

sons infected with serotypes that provide essentially the same evidence.

Further evidence of the validity and stability of the established serotypes was provided by reisolation of strains from human volunteers infected with 5 separate serotypes (Types 1, 2, 3, 5 and 6). In each of 13 subjects the serotype recovered was immunologically identical with that given.

The occurrence of heterotypic responses makes it possible to blame the wrong serotype in the etiology of individual cases on the basis of serum neutralization tests. Fortunately, the likelihood of this occurrence is not great in immunologic studies of cases encountered during a homogenous outbreak of illness.

Table 4. *Heterotypic Responses in the Complement-Fixation Test.**

Antigen	Infecting Virus						Totals
	type 1	type 2	type 3	type 4	type 5	type 6	
Type 1		5/8	9/9	6/9	2/2	3/5	25/33 (75.8%)
Type 2	6/6		7/9	9/9	2/2	4/5	28/31 (90.3%)
Type 3	5/6	5/8		7/9	2/2	3/5	22/30 (73.3%)
Type 4	4/6	6/8	7/9		2/2	4/5	23/30 (76.7%)
Type 5	6/6	5/8	7/9	8/9		4/5	30/37 (81.1%)
Type 6	5/6	5/8	7/9	8/9	2/2		27/34 (79.4%)

* Fraction = $\frac{\text{No. of persons with 4-fold CF antibody rise to heterotypic antigen}}{\text{total number of persons showing 4-fold homotypic rise.}}$

Group-Specific Complement-Fixing Antigens

Antibody responses produced by rabbit immunization and human infection with adenoidal-pharyngeal-conjunctival viruses revealed common antigens shared almost equally by all 6 serotypes. In Table 3 it can be seen that whereas human neutralizing antibody responses in the 6 persons were generally specific, complement-fixing responses were almost entirely nonspecific; however, the quantitative variations between strains should be noted. Table 4 gives additional data emphasizing the extent of crossreactions given in complement-fixation tests against 6 antigens by paired serums from more than 30 persons infected with the 6 serotypes. In all cases more than 70 per cent of the persons infected with any given strain showed fourfold heterotypic rises against the other antigen types. Of the 6 antigens Type 2 seemed to have the broadest antigenic pattern since 90 per cent of persons with infections with the other 5 types showed a rise to this type. The complement-fixation test, therefore, is of little value in identifying infections due to particular serotypes of adenoidal-pharyngeal-conjunctival viruses. However, as shown below, there is good evidence that responses to the common antigen were not produced by many other infectious agents, thus providing an easily performed serologic test of value in detecting infections with viruses of the adenoidal-pharyngeal-conjunctival group.

Occurrence of Viruses, Prevalence of Antibodies and Association with Human Illness

It has recently become quite apparent that simple associations of frequently occurring newly recognized viruses with illnesses, although furnishing research leads and basis for hypothesis, can no more establish an etiologic role than similar associations of common bacteria. Caution and the application of certain criteria[11,12] for determining etiologic significance of viruses, conceived and perhaps modeled after Koch's postulates, cannot be urged too strongly, particularly in the light of experience with other prevalent agents[13] and at a time when new viruses are being reported more rapidly than they can be accurately characterized. It seems essential to avoid generalizations about the clinical effects of entire groups of similar agents and to consider the clinical importance of each member of a group on the evidence that concerns only that agent. Careful characterizations in biologic and immunologic terms and adequate information concerning occurrence and prevalence of specific agents seem not only desirable but also necessary to an accurate assessment of the clinical significance of new viruses such as the adenoidal-pharyngeal-conjunctival agents.

Table 5 shows the clinical circumstances associated with the isolation of 143 separate strains that have been typed. With 2 exceptions, all available strains of Types 1, 2, 5 and 6 were recovered by culture of adenoids and tonsils. A Type 1 strain was recovered

from pharyngeal secretions of a two-year-old infant, taken on the first day of an acute febrile illness with exudative pharyngitis.[14] Specific antibodies appeared in convalescence. Type 5 was demonstrated in a laboratory technician suffering from an acute sore throat and earache without apparent fever; she had worked extensively with this agent several days before.

Types 3 and 4, on the contrary, have been recovered almost exclusively from persons with some kind of illness — chiefly respiratory illnesses. Our first encounter with Type 3 was in the nasal washings of human volunteers inoculated during the summer of 1953 with nasal secretions from a person experiencing an afebrile, runny-nose type of common cold.[8] Although similar afebrile "colds" developed in several volunteers from whom the agent was recovered attempts to link this agent with subsequent similar colds produced by serial passage of their nasal washings were unsuccessful. Although the Type 3 agent disappeared during the serial passage in volunteers the "colds" continued and were indistinguishable from those experienced by the volunteers infected with Type 3 virus. These findings suggest that Type 3 virus represented a kind of "fellow traveler" producing infection but not illness — the illness probably being due, in this case at least, to some other unknown agent or factor.

Shortly after this, Type 3 was demonstrated in the conjunctival secretions of 2 of our associates in whom unilateral conjunctivitis without fever or systemic illness developed. One infection occurred in a worker exposed to Type 3 virus in the laboratory, and the other in a pediatrician exposed to an infant, subsequently shown to be infected with Type 3 virus, who coughed into his face during a physical examination.[9] Dr. Ralph W. Ryan,* who examined both patients, described the conjunctivitis as follows:

> . . . each patient had a uniocular nonpurulent conjunctivitis, with lymph follicle hyperplasia most marked in the lower conjunctival cul-de-sac and with mild discomfort. There was no complaint of photophobia, the cornea was not involved, and vision was not affected. The disease cleared in approximately one week without evident response to chlortetracycline drops.

Subsequently, during February and again during the summer of 1954, outbreaks of acute respiratory illness characterized by fever, pharyngitis, conjunctivitis and infection with Type 3 virus became available for study.[9,10] These separate outbreaks can be considered only briefly here. In the first outbreak 3 children and 4 adults, patients and staff members of a hospital ward, manifested respiratory illnesses, several with conjunctivitis, within thirteen days of admission for study of a two-year-old girl with a febrile nasopharyngitis and conjunctivitis. Of the 8 patients 5 had fever (the temperature in 1 reaching 104°F.) for five or six days; 6 had nasopharyngitis. However, bacterial cultures of throats were negative for streptococcal organisms; 3 were positive for *Haemophilus haemolyticus*. Type 3 virus was isolated from the 5 patients from whom throat or conjunctival secretions were obtained. Serologic evidence of infection with Type 3 virus was demonstrated in all 8 patients.

During the past summer we had an opportunity to observe outbreaks of acute catarrhal pharyngitis and conjunctivitis in Northern Virginia.[10] Encountered initially in students of a summer day school and in their household contacts, the illness was subsequently observed in several other communities. Type 3 virus

TABLE 5. *Natural Occurrence of 143 Adenoidal-Pharyngeal-Conjunctival Virus Isolates Classified Immunologically.*

Clinical Circumstances	No. of Isolations					
	Type 1	Type 2	Type 3	Type 4	Type 5	Type 6
Adenoids & tonsils:						
Children	19	12			6	1
Adults	4			1		
Acute pharyngitis & conjunctivitis						
Throat swabs			42			
Conjunctival swabs			31			
Anal swabs			13			
Acute pharyngitis (throat swab)	1				1	
Acute respiratory disease in military recruits (nasal washings)				6		
Human volunteers with common colds (nasal washings)			4			
Case of Letterer-Siwe disease (lungs & mesenteric lymph node)			2			
Totals	24	12	92	7	7	1

*Acting chief, Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health.

was demonstrated in the throat or conjunctival secretions and anal excretions of 76 patients. Virus was not demonstrated in 85 controls who were not ill. An epidemiologic study reported separately[10] provided excellent evidence of an etiologic role for Type 3 virus. The conjunctivitis and the evident association of many cases with swimming pools suggested a relation with swimming-pool conjunctivitis[15]; however, the systemic clinical findings, the duration and character of the ocular findings and the absence of inclusions in conjunctival smears distinguished the illnesses observed in the Virginia outbreaks from swimming-pool and inclusion conjunctivitis. Previous reports of outbreaks of conjunctivitis with systemic illness associated with swimming pools by Derrick[16] in Australia and Cockburn in Greeley, Colorado,[17] describe illnesses quite similar to those observed by us in Virginia. Paired serums* were obtained from patients with typical cases studied by Cockburn during the Greeley outbreak. Substantial antibody rises in the complement-fixation test to the group antigen (Table 6) and type-specific antibodies in neutralization tests to Type 3 virus developed in each of 8 cases.

TABLE 6. *Rises in Complement-Fixing Antibody to Adenoidal-Pharyngeal-Conjunctival Virus Group (Type 7 Antigen) in Persons with Acute Pharyngitis and Conjunctivitis and with Undifferentiated Respiratory Diseases.*

Clinical Diagnosis	No. of Fourfold Rises	
	No. tested	Percentage
Acute pharyngitis and conjunctivitis (chiefly febrile):		
Outbreak in Clinical Center, National Institutes of Health, winter, 1954....	5/7	71.4
Outbreak in Northern Virginia, summer, 1954.....	14/15	93.3
Epidemic in Greeley, Colorado, summer, 1951*.....	8/8	100.0
Various respiratory diseases in children, Washington, D. C., winter, 1954†..	13/52	25.0
Military recruits, Great Lakes Naval Training Center, winter, 1954‡:		
Febrile respiratory illnesses.....	6/20	30.0
Atypical pneumonia.....	1/3	
Afebrile respiratory illnesses.....	1/19	5.3
Nonrespiratory illnesses.....	0/17	0.0

* Received through the courtesy of Morris Schaeffer, M.D., and F. S. Cheever, M.D.
† Received through the courtesy of Jean Lockhart, M.D., Joseph Engler, M.D., and Leroy Hoeck, M.D.
‡ Received through the courtesy of Commander John Seal, USN.

Type 3 virus was also recovered from lung and mesenteric-lymph-node tissue obtained at autopsy in a case of Letterer–Siwe disease. This is an interesting finding, but etiologic significance cannot be attributed to the simple associations observed in a single case.

*Received through the courtesy of Dr. Morris Schaeffer, medical director, Communicable Disease Center, Department of Health, Education and Welfare, Montgomery, Alabama, and Dr. F. S. Cheever, professor of microbiology, Graduate School of Public Health, University of Pittsburgh.

Type 4 (RI-67) virus was encountered 7 times—in the adenoid of a thirty-six-year-old man, and in nasopharyngeal secretions of 6 military recruits with respiratory illnesses. Collaborative studies[18] (as yet incomplete) with the research staff of NAMRU No. 4 of respiratory illnesses occurring during January and February, 1954, in Navy recruits at the Great Lakes Naval Training Station revealed a rise in complement-fixing antibodies in 8 persons (Table 6), 6 of whom had febrile respiratory illnesses characterized by complaints of sore throat, nasal congestion, nasal discharge and cough. Tonsillitis, pharyngitis, hoarseness and coryza were prominent signs. Another patient had a similar illness, with roentgenologic evidence of pneumonitis. The eighth patient had only a simple coryza without fever, which was diagnosed as "common cold." Nasal washings were available on 6 of the 8 recruits with antibody rises, and all 6 contained Type 4 virus.

Information concerning the prevalence of prior infections in populations at risk is of cardinal importance in determining the real significance of common newly recognized agents observed in association with frequently occurring illnesses. We have shown that the neutralization tests performed in tissue culture[5] provide evidence of prior infection with the adenoidal-pharyngeal-conjunctival agents that appear to be, for the most part, type specific. Figure 1 presents in graphic form the prevalence of type-specific antibodies against 6 prototype viruses in the serums (diluted 1:4) of more than 200 persons in 5 age groups. Since large numbers of serums were not available from any one homogeneous population in the Washington, D.C., area, serums from indigent persons

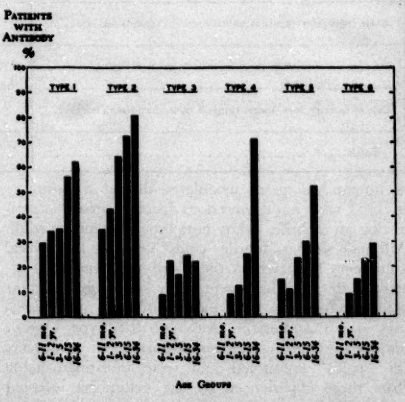


FIGURE 1. *Neutralizing Antibodies to Adenoidal-Pharyngeal-Conjunctival Viruses in Different Age Groups of Clinic Populations, Washington, D.C. (1950-1954).*

attending free clinics of three hospitals* were tested. The persons under sixteen years of age were generally ill. The group over sixteen consisted of gravid patients; therefore, the findings were influenced by undetermined factors of selection. However, in all cases the serums from patients were taken within one to five days of onset of the clinical conditions that had brought the patient to the hospital clinic. Thus, the current illness or clinical state would not be expected to have influenced prior specific antibodies against the viruses. Despite these deficiencies, Figures 1 and 2 have considerable value in depicting antibody prevalence, particularly since similar studies of several other populations, none in themselves extensive enough to justify detailed descriptions, gave results entirely consistent with those presented.

Antibodies to Types 1 and 2 were found to be quite prevalent in younger age groups, positive reactions occurring in 55.8 per cent and 72.3 per cent, respectively, of the persons six to fifteen years of age. Surprisingly, over 30 per cent of infants six to eleven months of age already possessed antibodies to these two types. These findings are interesting but were not wholly unexpected since a majority of isolations of adenoidal-pharyngeal-conjunctival viruses from adenoids and tonsils removed from children attending the same clinics were classified in Serotypes 1 and 2. Reactions against Types 3 and 6 were significantly less in patients sixteen to thirty-four years of age (consisting primarily of young gravid women), suggesting that for some years before 1954 these strains were not very prevalent in this area. Of interest is the fact that Type 6 was encountered only once and Type 3 not at all in adenoids and tonsils. However, as indicated above, infections with Type 3 were quite common in this area in certain epidemiologic groups during the summer of 1954. The sharp rise in the frequency of antibodies to Type 4, from 25 per cent in the group six to fifteen years of age to 71.1 per cent in the group sixteen to thirty-four years of age suggests that this type was possibly epidemic fifteen years or more previously but not since then. Alternative, but much less likely, explanations would postulate resistance at early ages and susceptibility acquired with increasing age to Type 4, or the existence of special epidemiologic circumstances favoring infection of gravid patients over sixteen years of age. Factors perhaps influencing these figures and, therefore, the interpretations would be the persistence of homotypic antibodies after infection and the occurrence of unknown degrees of heterotypic responses to infection.

The cumulative occurrence in the various age groups of antibodies against one or more types is illustrated in Figure 2. Antibodies were already present in the majority of infants six to eleven months of age, more than 50 per cent showing antibodies against 1 or more types. A substantial increase in antibodies occurred in the patients one to two years of age, but very little additional increase occurred in those three to five years old. Marked increases were observed in the groups six to fifteen and sixteen to thirty-four years of age, in which the majority of persons had antibodies to 3 or more types. Unfortunately, groups of older persons in any respect comparable to the clinic population represented in Figures 1 and 2 were not available. However, we tested more than 15 persons forty to seventy years of age, nearly all of whom

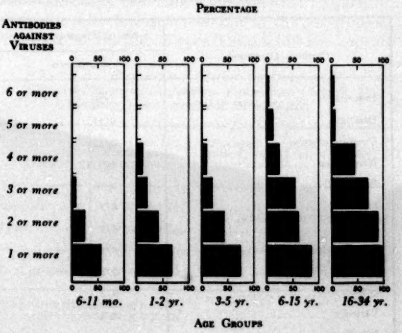


Figure 2. *Cumulative Neutralizing Antibodies to 6 Types of Adenoidal-Pharyngeal-Conjunctival Viruses in Different Age Groups of Clinic Populations, Washington, D.C. (1950-1954).*

were found to have neutralizing antibodies to at least 4 types: the majority had antibodies to 5 or more types. Thus, it appears that infections may continue to occur after the age of thirty-four, at least until neutralizing antibodies are acquired to nearly all the six types thus far recognized.

Value of the Complement-Fixation Test in Epidemiologic Studies of Occurrence of Viruses

We have shown that rises in complement-fixing antibodies to the common adenoidal-pharyngeal-conjunctival antigen developed after infection with these viruses. Although of no value in determining the specific type of virus causing infection, the complement-fixation test provided a generally available technic, limited only by antigen supplies, for detecting infections with the adenoidal-pharyngeal-conjunctival group. Table 7 shows that rises in complement-fixing antibody were conspicuously absent in 139 of 141 patients with a variety of different diseases besides undifferentiated respiratory illnesses. One of 26 persons with proved influenza occurring during the late winters in 1950 and 1953 showed a greater than fourfold rise in titer during convalescence. This could well have represented a mixed infection, an eventuality that might have been expected to occur

*Obtained through the courtesy of Dr. Jean Lockhart, Children's Hospital, Washington, D. C., Dr. Joseph Eagler, senior assistant surgeon, Laboratory of Infectious Diseases, National Microbiological Institute, National Institutes of Health, and Dr. Leroy Hoeck, director of pediatrics, District of Columbia General Hospital, Washington, D. C.

with even greater frequency. A questionable twofold rise in 1 case of herpangina was judged insufficient to represent a true convalescent response to infection with the viruses and probably represented a minor fluctuation in antibody levels. These data suggest that, despite widely prevalent complement-fixing and neutralizing antibodies to the adenoidal-pharyngeal-conjunctival viruses, anamnestic responses do not often follow infections with other agents.

TABLE 7. *Complement-Fixing Antibody Responses to Adenoidal-Pharyngeal-Conjunctival Virus Group (Type 1 Antigen) in Persons with Illnesses other than Undifferentiated Respiratory Diseases.*

Clinical Diagnosis	No. of Twofold Rises / No. Tested
Influenza*	1/26
Diarrhea	0/11
Gingivostomatitis	0/21
Herpangina	1(?)/12
Poliomyelitis	0/10
Mumps	0/7
Rubeola	0/9
Infectious hepatitis	0/2
Epidemic pleurodynia	0/11
Q fever	0/4
Varicella	0/3
Infectious mononucleosis	0/3
Primary atypical pneumonia with rise in cold agglutinins†	0/8
Croup	0/4
Nonbacterial meningitis	0/10
Total	2/141 (1.4%)

* Confirmed in laboratory.
† Received from Dr. Frank Horsfall, Jr., & Dr. William S. Jordan.

On the other hand Table 6 shows that numerous fourfold, or greater, rises occurred in convalescent serums from persons involved in epidemics of acute pharyngitis and conjunctivitis, and in serums acquired in surveys of undifferentiated respiratory illnesses in pediatric and military groups. Rises occurred in 5 of 7 and 14 of 15 persons with an entity described as acute pharyngitis and conjunctivitis,[9,10] all of whom were shown by other tests to be infected with Type 3 virus. Eight persons from the 1951 Greeley outbreak,[17] described above, gave specific responses in the neutralization test against Type 3 virus only, and all showed excellent rises against the complement-fixing antigen of the Type 1 virus. They also gave almost identical results when tested with a Type 3 complement-fixing antigen. Similarly, of 8 recruits with respiratory illnesses showing a rise in the complement-fixation test, 3 were tested in neutralization and demonstrated rises in antibodies to Type 4 virus, and from all 6 on whom specimens were available, Type 4 was recovered.

These findings suggest that the complement-fixation test using the common adenoidal-pharyngeal-conjunctival antigen is of considerable value as a preliminary, easily applied method for detecting infection, a hypothesis that has been repeatedly tested and amply justified in various clinical and epidemiologic studies.[6,9,10] Such a test might well be incorporated in the battery of serologic procedures routinely performed in clinical and public-health laboratories.

Thus, during the winter of 1954, 13 of 52 paired serums collected in hospital clinics from children with various respiratory illnesses tested by complement fixation gave presumptive evidence of infection with adenoidal-pharyngeal-conjunctival viruses of undetermined immunologic types. Of further interest in this survey was the fact that whereas neutralization tests against 6 types generally revealed rises against 1 or more types, in several cases in which rises in neutralizing antibodies occurred against several types, it was difficult to establish precisely the type that produced the antibody response. Several of the patients showing excellent complement-fixing rises from negative to a titer of 1:128, or higher, failed to manifest antibody rises against any of the 6 types of sufficient magnitude to suggest that they represented homotypic responses. This, and evidence obtained from other infants in whom high levels of complement-fixing antibodies developed by six months of age (having been negative six to eight weeks after birth), suggested that additional types of adenoidal-pharyngeal-conjunctival viruses remain to be characterized.[19] In any event, the complement-fixation test appeared to have little value as an index of the prevalence of type-specific infections. Our evidence indicated that a high complement-fixation level may represent prior infection with one or any number of types. The level apparently depended on how recently a specific infection had occurred. Quite as evident was the fact that older persons (forty years or older) with neutralizing antibodies to 4 or more strains frequently gave completely negative results to the complement-fixation test,[10] thus revealing complete disassociation of these 2 types of demonstrable antibodies in such persons.

Studies in Human Volunteers

All 6 types of viruses were administered intranasally to human volunteers.[8] Both nasopharyngeal secretions and tissue-culture fluids containing active virus were used as inoculums. Few objective manifestations of illness resulted in the groups injected with virus, and these effects only rarely exceeded similar clinical manifestations observed in controls. However, most of the volunteers presented evidence of active infection, as indicated by sharp rises in the complement-fixing and neutralizing antibody levels and by the appearance of virus in nasopharyngeal secretions taken three to six days after injection.

Failure to produce overt illnesses could be explained by the presence of pre-existing neutralizing antibodies in the serums of a majority of the volunteers, but many volunteers gave no evidence of pre-existing serum antibodies.

Besides furnishing precise evidence concerning the immunologic specificities of the different adenoidal-pharyngeal-conjunctival viruses, studies in human volunteers contributed the following information: that an infectious process resulted from intranasal injections with either infected human secretions or tissue-culture fluids; that infectious processes could be superimposed on persons with evidence of previous infection with the serotype given; and that infections with the viruses were frequently induced without the production of overt illnesses.

"Unmasking" of Viruses

It is of considerable interest that 5 of the 6 virus types were demonstrated in the tissue of adenoids and tonsils removed at surgery by growing epithelium from such tissue for prolonged periods in roller-tube cultures. Table 8 shows that whereas these agents could be detected by means of the "unmasking" procedure of growing the tissue themselves, they could not be isolated from nasopharyngeal swabs or from suspensions of adenoids and tonsils of the same persons by the more conventional method of inoculating such materials into highly susceptible HeLa-cell cultures. A possible explanation of the greater sensitivity of the "unmasking" procedure might be deduced not only from the fact that the patients undergoing tonsillectomy and adenoidectomy possessed serum antibodies against the virus types later recovered from them but also because such antibodies were demonstrated in the suspensions of adenoidal and tonsillar tissues.[8] It seems likely, then, although this has not yet been demonstrated, that these antibodies would be gradually washed from the culture tube and thus from the outgrowing cells during several weeks of biweekly changes of tissue-culture fluids.

Discussion

A most important consideration is the possible significance of the adenoidal-pharyngeal-conjunctival group of viruses in the production of human disease. Hilleman and Werner,[6] reporting a new virus, RI-67, recovered from the nasopharyngeal secretions of military personnel with acute respiratory illnesses, suggested that this agent played a causative role in many cases of acute respiratory disease and in atypical pneumonia not characterized by the development of cold agglutinins, both of which are clinical entities of considerable importance in military medicine. Our experience with biologically and immunologically identical agents, classified by us as Type 4 in the adenoidal-pharyngeal-conjunctival group, are consistent with this hypothesis, 6 of 7 isolates of this type having been obtained from Navy recruits with acute respiratory diseases.

Repeated studies of outbreaks of febrile pharyngitis and conjunctivitis have provided excellent evidence that Type 3 virus represents a prolific cause of acute respiratory illnesses in man.[9,10]

We have also presented serologic evidence that the other 4 types of viruses produce infections in man. However, we have acquired few data concerning the illnesses caused by these infections. Infections with Types 1 and 2, on the basis of present evidence, appeared extremely common, occurring most frequently during the first few years of life in the geographic areas thus far studied. Types 5 and 6 did not appear to have been extremely prevalent during recent years in those areas. Therefore, to observe the clinical effects of infection with some of these types it seems necessary to emphasize the primary infections occurring during infancy and early childhood or to search diligently for outbreaks — in which other types might be involved — that might be expected to occur because of high levels of susceptibility in the populations at risk.

Table 8. *Comparison of Methods for Isolation of Adenoidal-Pharyngeal-Conjunctival Viruses from Children Undergoing Tonsillectomy and Adenoidectomy.*

Tissue	Isolation by Unmasking in Tissue Cultures	Isolation from Tissue Suspensions	Isolation from Throat Swabs
Adenoids.....	50/88 (56.9%)		
Tonsils.....	13/33 (39.4%)	1/25* (4.0%)	0/18† (0.0%)
Total patients ..	54/94 (57.5%)		

*15 positive by unmasking technic.
†11 positive by unmasking technic.

Quite apart from their importance in the genesis of acute illness is the question of their possible role in the chronic diseases of the nasopharynx that result in surgical removal of adenoids and tonsils. Although there is at present no convincing evidence that the persistence of these agents in such tissues represents a factor in disease and hypertrophy of those tissues, an exploration of this possibility seems warranted.

The existence of 6 and possibly more serotypes satisfying criteria for inclusion in this commonly occurring group of agents makes it highly desirable that some consistent terminology be used for designating the group. The term "adenoid-degenerating" agents used in the initial report on these agents cannot be regarded as truly descriptive of the group as it is now constituted. Unfortunately, it is not yet possible to link these agents with any single human pathologic entity — indeed, it appears likely that different types of these agents cause distinct nosologic entities. For this reason we have selected "adenoidal-pharyngeal-conjunctival" agents as a term that is noncommittal with respect to human disease and yet

sufficiently descriptive to indicate the important anatomic sites where the viruses are found. The use of this generic term for a large group of viruses does not preclude whatever future application of specific designations for members of the group may be dictated by future definitive clinical and epidemiologic information.

At present the most important properties to be considered in the definition of the group, as well as the criteria for including new candidate prototypes within the group, are as follows: complement-fixing antigen common to the group; characteristic cytopathogenic effects in human epithelium and in HeLa cells; apathogenicity for common laboratory animals; and ether resistance.

Definitive inclusion of candidate isolates within serotypes of the group requires that reciprocal cross-neutralizations be performed with well defined prototypes. This precaution seems most necessary because, in our experience, one-directional tests occasionally lead to false typing, particularly if the candidate agent is not tested against all available prototype serums. It is pertinent to point out that the validity of the present 6 types has been further established by human antibody responses to infections with all 6 types. Types 5 and 6 are still regarded as a somewhat tentative classification because only 1 human response to each of these types has so far been studied and because only 1 representative of Type 6 has been recognized.

Summary and Conclusions

New respiratory-system viruses have been isolated in tissue culture from adenoid and tonsillar tissue removed at surgery and from nasopharyngeal and conjunctival secretions and feces of persons with respiratory illnesses. These new viruses are designated as adenoidal-pharyngeal-conjunctival agents, indicating the important anatomic sites in which they are found. One hundred and forty-three strains have been segregated into 6 immunologic types, and additional types probably exist. All types grow readily, producing similar and unique cytopathogenic effects, in human epithelial cells and in HeLa cells available commercially. They are resistant to ether and antibiotics. In human beings and in rabbits they produce potent, type-specific neutralizing antibodies and lesser amounts of heterotypic responses. Complement-fixing antigens and antibodies produced in comparatively large amounts are group specific but not type specific, being shared to about the same extent by all 6 types.

All 6 types cause frequent infections in man, beginning at an early age. Serologic surveys in the Washington, D.C., area indicate that 50 per cent of infants six months to one year of age have been infected with at least 1 type. By the age of fifteen the average person has had infections with several types. Most persons have antibodies to 4 or more types by the age of thirty-four, and a few have antibodies against all 6 types. The amount and specific kind of illnesses produced by these infections are the subject of intense investigations. There is convincing evidence that Types 3 and 4 cause specific respiratory illnesses. Type 4 (Hilleman and Werner's RI-67 agent) apparently produces respiratory illnesses in military personnel described as acute respiratory disease and primary atypical pneumonia.

Type 3 has been recovered in numerous cases of acute nasopharyngitis and conjunctivitis occurring during a winter outbreak on a hospital ward and a summer outbreak in a country day school. Epidemiologic studies appear to establish Type 3 as the causative agent of this apparently specific clinical entity. Types 1 and 5 have also been found in cases of acute pharyngitis, but more evidence is needed to establish the role of these and other types in human disease.

These viruses have been isolated from adenoids and tonsils of a majority of persons undergoing tonsillectomy and adenoidectomy by growing of those tissues in tissue culture (43 strains classified in 5 immunologic types have been obtained from these sources), suggesting that a possible role in persistent chronic disease of tonsils and adenoids should be investigated. Possibly of more importance is the demonstration of viruses in tissues containing specific antibody against them by the simple expedient of growing the infected tissues for prolonged periods. This method of "unmasking" viruses represents a highly sensitive and essentially new technic for isolating viruses.

References

1. Stuart-Harris, C. H. *Influenza.* 235 pp. London: Edward Arnold, 1953.
2. Commission on Acute Respiratory Diseases. Acute respiratory disease among new recruits. *Am. J. Pub. Health* 36:439-450, 1946.
3. Andrewes, C. H., In Stuart-Harris.[1]
4. Rowe, W. P., et al. Isolation of cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. *Proc. Soc. Exper. Biol. & Med.* 84:570-573, 1953.
5. Rowe, W. P., Huebner, R. J., Hartley, J. W., Ward, T. G., and Parrott, R. H. Studies of adenoidal-pharyngeal-conjunctival (APC) group of viruses. *Am. J. Hyg.* (in press).
6. Hilleman, M. R., and Werner, J. H. Recovery of new agent from patients with acute respiratory illness. *Proc. Soc. Exper. Biol. & Med.* 85:183-188, 1954.
7. Neva, F. A., and Enders, J. F. Isolation of cytopathogenic agent from infant with disease in certain respects resembling roseola infantum. *J. Immunol.* 72:315-321, 1954.
8. Ward, T. G., Huebner, R. J., and Rowe, W. P. Unpublished data.
9. Parrott, R. H., Rowe, W. P., Huebner, R. J., Bernton, H. W., and McCullough, N. B. Outbreak of febrile pharyngitis and conjunctivitis associated with Type 3 adenoidal-pharyngeal-conjunctival virus infection. *New Eng. J. Med.* 251:1087-1090, 1954.
10. Bell, J. A., et al. Unpublished data.
11. Rivers, T. M. Viruses and Koch's postulates. *J. Bact.* 33:1-12, 1937.
12. Huebner, R. J. Studies in virus diseases, human and animal: guidance criteria. *Pub. Health Rep.* 69:183, 1954.
13. Huebner, R. J., et al. Importance of Coxsackie viruses in human disease, particularly herpangina and epidemic pleurodynia. *New Eng. J. Med.* 247:249-256 and 285-289, 1952.
14. Parrott, R. H., Rowe, W. P., and Huebner, R. J. Unpublished data.
15. Thygeson, P. In Rivers, T. M. *Viral and Rickettsial Infections of Man.* Second edition. 719 pp. Philadelphia: Lippincott, 1952. Pp. 471-475.
16. Derrick, E. H. Swimming-bath conjunctivitis with report of three probable cases and note on its epidemiology. *M. J. Australia* 2: 334-336, 1943.
17. Cockburn, T. A. Epidemic of conjunctivitis in Colorado: associated with pharyngitis, muscle pain, and pyrexia. *Am. J. Ophth.* 38:1534-1539, 1955.
18. Seal, J. R., Ward, T. G., Rowe, W. P., and Huebner, R. J. Unpublished data.
19. Huebner, R. J., and Rowe, W. P. Unpublished data.

OUTBREAK OF FEBRILE PHARYNGITIS AND CONJUNCTIVITIS ASSOCIATED WITH TYPE 3 ADENOIDAL-PHARYNGEAL-CONJUNCTIVAL VIRUS INFECTION*

ROBERT H. PARROTT, M.D.,† WALLACE P. ROWE, M.D.,‡ ROBERT J. HUEBNER, M.D.,§
HORACE W. BERNTON, M.D.,¶ AND NORMAN B. MCCULLOUGH, M.D.‖

BETHESDA, MARYLAND

ON February 11, 1954, a two-year-old girl with acute febrile rhinitis, pharyngitis and conjunctivitis was admitted to the Infectious and Parasitic Disease Service of the Clinical Center at the National Institutes of Health, as a subject in the clinical and etiologic study of acute respiratory illnesses. During her admission examination she coughed in the face of the attending pediatrician, in whom, six days later, mild rhinitis, pharyngitis and unilateral conjunctivitis developed. Eight days after the admission of this child, the pediatric nurse who attended her and a seven-year-old girl who occupied the other bed in her hospital room also manifested febrile pharyngitis. During the next week similar cases of fever with rhinitis and pharyngitis occurred in an ambulatory adult study patient and in 2 ambulatory pediatric patients. Another pediatrician had rhinopharyngitis without fever thirteen days after admission of the first patient.

This paper describes the clinical features of the illness in these 8 cases and reports the evidence in each of them of infection with a newly recognized viral agent, adenoidal-pharyngeal-conjunctival virus, Type 3.[1-4]

GENERAL ASPECTS

The series of illnesses studied occurred on a hospital service composed of 13 two-bed rooms arranged along one side of a corridor. All the children's rooms are at one end of the hall. A playroom across the corridor is available for the use of any ambulatory pediatric study patients. On rare occasions adult patients play with the children; there is a solarium where adults and children occasionally mingle for television viewing.

The medical staff of 7 includes 2 pediatricians. In general, other physicians than these 2 have contact with the children only during formal rounds. The auxiliary staff of about 20 is so divided into teams that 3 or 4 persons have considerably more contact with children than the others. During at least a month before the onset of the illnesses described, febrile respiratory disease had not been unusually frequent in patients or members of the staff.

*From the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute.

†Senior assistant surgeon, Laboratory of Clinical Investigation, National Microbiological Institute.

‡Senior assistant surgeon, Laboratory of Infectious Diseases, National Microbiological Institute.

§Medical director and chief, Virus and Rickettsial Diseases Section, Laboratory of Infectious Diseases, National Microbiological Institute.

¶Senior assistant surgeon, Laboratory of Clinical Investigation, National Microbiological Institute.

‖Medical director and chief, Laboratory of Clinical Investigation, National Microbiological Institute.

LABORATORY METHODS

Sterile cotton swabs of the posterior pharynx or conjunctival membranes of patients were tested for the presence of adenoidal-pharyngeal-conjunctival viruses by methods outlined in a separate publication.[3] Paired acute (or pre-illness) and convalescent serums from the patients were tested for complement-fixing and neutralizing antibody against adenoidal-pharyngeal-conjunctival virus, Type 3, by methods outlined elsewhere.[3]

Multiple throat cultures for bacteria were taken in all cases during acute illness; between February 19 and 24, throat cultures for bacteria were also obtained from all the members of the medical and nursing staff. The posterior pharynx was swabbed with a sterile cotton applicator; a slide was prepared for Gram's staining, and inoculations were made on rabbit-blood agar and into trypticase soy broth. After incubation the cultures were examined appropriately for pathogenic bacteria by a competent research bacteriologist.

OCCURRENCE OF CASES

Eight cases of upper respiratory disease in patients and staff members occurred from February 11 to February 26, 1954. These cases included 4 children and 4 adults who were in contact with the children. The chronology of occurrence of cases and certain clinical features are summarized in Table 1.

CASE 1. J.F., a 2-year-old girl, was admitted to the service on February 11. Two days previously fever, vomiting, rhinorrhea, cough, anorexia and irritability had developed. At the time of admission she had a temperature of 104°F., bilateral palpebral and bulbar conjunctivitis, bilateral catarrhal otitis media, slight enlargement and marked inflammation of the tonsils and moderate cervical adenopathy at the angle of the mandible. A whitish-grey exudate was seen on 1 tonsil on the 5th day of illness; this persisted for approximately 2 days. X-ray evidence of haziness of the ethmoid and maxillary sinuses was present and persisted for almost 2 weeks. Fever lasted for 4 days after hospitalization, pharyngeal inflammation for 9 days, and lymphadenopathy for 3 weeks. Adenoidal-pharyngeal-conjunctival virus, Type 3, was recovered from a throat swab on the 5th day of illness. During the illness there was a rise in titer of serum complement-fixing antibody for Type 3 virus from less than 1:8 to over 1:128 and of neutralizing antibody from less than 1:4 to over 1:16.

CASE 2. On the day of admission J.F. accidentally coughed into the face of a staff pediatrician, R.P., who immediately washed the sputum from his eyes and face. Six days later mild nasal congestion, pharyngitis and moderately severe unilateral bulbar and palpebral conjunctivitis developed. There was no fever. The ocular inflammation included hemorrhagic tendencies for 2 days; there was very little pain and no pruritus. No bacterial organisms were isolated from the eye by culture. The inflammatory signs

persisted for 6 days; there was no involvement of the opposite eye. An eye swab obtained on the 3d day of illness contained Type 3 virus. Although there was no increase in the serum complement-fixing antibody titer, that for neutralizing antibody rose from less than 1:4 to over 1:64 during the illness.

CASE 3. Eight days after the admission of J.F. her hospital roommate, J.K., a 7-year-old girl recovering from Sydenham's chorea, exhibited fever with rhinitis, exudative pharyngitis, cervical lymphadenopathy and mild bilateral conjunctivitis. Fever and physical signs persisted for about 5 days (Fig. 1). Before the onset of this illness, she had been permitted to be in the common playroom for general activity and thus had been in contact with most of the other children on the service. No material was available for virus isolation, but during convalescence her serums showed a rise in complement-fixing titer from less than 1:8 to over 1:256 and in neutralizing antibody from less than 1:4 to over 1:16 for adenoidal-pharyngeal-conjunctival virus, Type 3.

CASE 4. Eight days after the admission of J.F., J. McC., a 28-year-old nurse who had worked with Cases 1 and 2, as well as with other children, contracted an acute febrile disease with chills, pharyngitis, cervical lymphadenopathy and liver tenderness (Fig. 2). The illness was severe enough to require hospitalization. Fever and other signs persisted for 5 or 6 days. On the 3d hospital day bromsulfalein retention was 10 per cent in 45 minutes, but on the 10th day it was 3 per cent. Flocculation tests for liver function and serum bilirubin were normal at these times. Type 3 virus was isolated from a throat swab taken on the 5th day of symptoms. Complement-fixing antibody titer for Type 3 virus rose from less than 1:8 to over 1:128, and neutralizing antibody from less than 1:4 to over 1:16 during convalescence.

TABLE 1. *Clinical Features of Illness in 8 Persons Infected with Type 3 Virus.*

Case No.	Age	Sex	Contact with Other Cases	Date of Onset of Illness	Clinical Features							Comment
					Maximum Temperature	Duration of Fever	Severity of Respiratory Symptoms*	Pharyngitis	Rhinitis	Cervical Lymphadenopathy	Conjunctival Injection	
	yr.				°F.	days						
1	2	F	Initial case; no similar illness in home contacts.	Feb. 9	104.7	6	++++	Present	Present	Present	Present	Treated with penicillin & Gantrisin
2	30	M	Pediatrician (Case 1 coughed in face)	Feb. 17	(Normal)	—	+	Present	Present	Present†	Present (severe)	
3	7	F	Hospital roommate of Case 1; in playroom until ill.	Feb. 19	104.0	6	++	Present	Present	Present	Present	Treated with penicillin & Gantrisin
4	28	F	Pediatric nurse	Feb. 19	102.6	6	+++	Present	Absent	Present	Absent	Treated with triple sulfonamide; transient liver tenderness.
5	25	F	Ambulatory (active)	Feb. 20	104.0	3½	+++	Absent	Present	Present	Absent	Transient liver tenderness
6	1	F	In playroom	Feb. 22	102.9	4½	++	Present	Present	Absent	Present	
7	28	M	Pediatrician	Feb. 24	(Normal)	—	+	Present	Present	Absent	Absent	
8	2	F	In playroom; hospital roommate of Case 6.	Feb. 27	102.2	3	++	Present	Present	Absent	Absent	On cortisone for adrenal disease

*+ to ++++.
†Later disappeared.

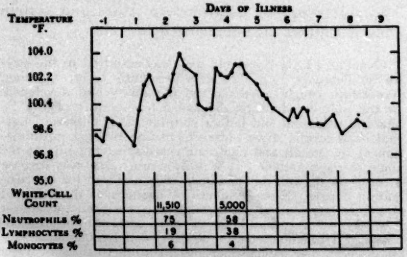


FIGURE 1. *Clinical Course in Case 3.*

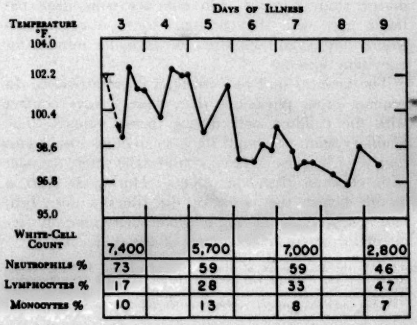


FIGURE 2. *Clinical Course in Case 4.*

CASE 5. Nine days after the admission of J.F., M.T., a 25-year-old woman under study for sarcoidosis, had fever, malaise, headache, chilliness and sweating. Physical signs included rhinitis and tender cervical adenitis. Liver tenderness was present on the 3d and 4th days of illness. Fever persisted for 5 days. On the 5th hospital day bromsulfalein retention was 21 per cent in 45 minutes; liver flocculation and the serum bilirubin were normal at this time. (During a previous hospitalization bromsulfalein retention had been 5 per cent.) On the 11th hospital day bromsulfalein retention was 2 per cent. Before the febrile illness she had been ambulatory and relatively free in visiting about the service, but remembered no direct contact with Case 1. The throat swab taken on the 4th day of fever yielded an isolation of Type 3 virus. During convalescence antibody titer against this virus rose from less than 1:8 to over 1:128 by complement-fixation tests and from less than 1:4 to over 1:16 by neutralization tests.

CASE 6. On the 11th day after J.F. was admitted to the service, M.L., a 1-year-old girl under study because of a predisposition to respiratory infections, experienced a febrile illness with rhinitis, pharyngitis and bilateral purulent conjunctivitis lasting for 5 days. She had been present on the service during the time of occurrence of the former cases and had been exposed to Cases 2, 3 and 4 for several days before the onset of their illness. Type 3 virus was recovered from a throat swab taken on the 2d day of the illness. Another throat swab on the 8th day did not contain virus. Serums showed a rise in titer against Type 3 virus from less than 1:8 to over 1:256 in the complement-fixation test and from less than 1:4 to over 1:16 in the neutralization test during convalescence.

CASE 7. Thirteen days after admission of J.F., the other staff pediatrician, G.M., a 28-year-old man, had symptoms of nasal congestion and pharyngitis without fever. He had had close contact with Case 6 and occasional contact with the other pediatric patients. A throat swab obtained on the 1st day of illness contained Type 3 virus. A single serum obtained on the 21st day after onset of symptoms contained a relatively high titer of neutralizing antibody (over 1:16) for Type 3 virus. No acute or pre-illness serum was available.

CASE 8. Fifteen days after J.F. was admitted to the service R.H., a 21-month-old girl who was on continuous cortisone therapy for adrenal hyperplasia and whose serum was deficient in gamma globulin, became ill with fever, rhinitis and pharyngitis of moderate severity that lasted for 3 days. She had previously been exposed to Cases 2, 3, 4 and 6. Specimens were not available for attempts at virus isolation. Serum obtained before illness and on the 12th day after onset revealed no complement-fixing antibody at a 1:8 dilution. Neutralizing antibody for Type 3 virus rose from less than 1:2 to over 1:8 during this period.

CLINICAL FEATURES

In summary, the illnesses observed in these 8 patients had the appearance of a distinct nosologic entity with somewhat variable features. Fever for five or six days was observed in 6 patients. Pharyngitis occurred in 7, with exudate in 2. Some degree of rhinitis was noted in 7 patients, and in 1 (Case 7) the diagnosis suggested was the "common cold." Definite cervical lymphadenopathy was present in 5 cases, and conjunctival inflammation in 4. Three patients had transient liver enlargement, accompanied by tenderness in 2. Antibiotics and sulfonamides apparently did not significantly influence the clinical course of the several patients for whom they were employed.

OTHER PERTINENT LABORATORY FINDINGS

Total white-cell counts, taken early in the illness in 6 of the 8 cases, ranged from 7400 to 16,400, with counts higher than 11,000 in 4. During the early period of the illness there was a slight tendency to neutrophilia. As symptoms progressed, differential counts returned to normal, and mild leukopenia developed in most patients.

There was no confirmed isolation of beta-hemolytic streptococci in any case. *Haemophilus haemolyticus* was present in the pharynx of 3 cases (Cases 2, 5 and 8). Of the 19 staff members who were not ill 2 were found to be harboring beta-hemolytic streptococci, and 4 *H. haemolyticus* in the nasopharynx.

Paired acute and convalescent serums from 4 patients (Cases 1, 2, 4 and 5) showed no rise in antistreptolysin-O titer. There was also no rise in hemagglutination-inhibition titer against 4 strains of influenza virus known to have been prevalent in the Washington metropolitan area in recent years (B/LEE/40, A/FLW/1/52, A/Va/1/53, C/1233).*

OTHER PATIENTS AND STAFF

In the two weeks after the onset of illness in the cases discussed above, 3 minor respiratory illnesses occurred in patients who were confined to bed in their own hospital rooms. One child with chronic ulcerative colitis, J.M.F., eight years of age, had mild afebrile rhinitis for two days beginning on March 3. N.N., a thirty-two-year-old woman with subacute bacterial endocarditis, experienced mild afebrile rhinitis and pharyngitis with slight cervical lymphadenopathy and liver tenderness on March 9. Her signs lasted for two days. E.B., a twenty-seven-year-old woman, had afebrile coryzal symptoms with liver tenderness for four days beginning on March 11. She had been in the hospital only four days before the onset of these signs. None of these patients had fever or conjunctivitis; their clinical illnesses were very mild.

Adenoidal-pharyngeal-conjunctival virus was not recovered from throat swabs taken on these 3 patients within the first three days of illness. None of the serums showed rises in complement-fixing or neutralizing antibody for Type 3 virus during convalescence. Each of them had a comparatively elevated neutralizing antibody titer (greater than 1:16) at the onset of the respiratory illness.

From February 11 to March 15 there were 4 children and 3 adults on the ward who had no fever and no signs of respiratory disease, and no antibody responses to Type 3 virus developed during this period. Two of these children were in isolation, and 2 had minimal exposure to other children. One of the adults was confined to bed, and 2 were ambulatory but not very active. No respiratory illnesses other than those recorded above were reported in members of the staff, or in 2 other adult patients from whom serums were not available for testing. There

*These tests were carried out by Dr. Dorland Davis, chief, Laboratory of Infectious Diseases, National Microbiological Institute, National Institutes of Health.

was no increased frequency of respiratory disease on other services in the Clinical Center.

Discussion

It is obvious that one must exert considerable caution in attributing etiologic significance to the association of a clinical illness with a commonly occurring viral agent. This is particularly true with a virus such as one of the adenoidal-pharyngeal-conjunctival group, whose existence and certain of whose microbiologic characteristics have only recently been reported and whose relation to disease is as yet unconfirmed.[1-3] Nevertheless, several aspects of the clinical illness reported here and the evidence for infection with Type 3 virus in the persons with illness (Table 2) support the hypothesis that there is an etiologic relation:

At least 6 of the initial 8 patients in this report had symptoms and signs that were strikingly similar (Cases 1, 3, 4, 5, 6 and 8). The 2 physicians (Cases 2 and 7) had symptoms that were similar but less severe and of shorter duration. The facts that all these cases were associated by direct or indirect contact and that the illness in each began within a limited period further suggest that the illnesses were manifestations of a distinct clinical and epidemiologic entity.

All 8 patients gave evidence of infection with Type 3 virus. From 5 (Cases 1, 2, 4, 5 and 6) the virus was recovered during the acute stage of illness, and antibody responses were demonstrated during convalescence. Two others (Cases 3 and 8), from whom materials for isolation attempts were not available, showed rises in antibody titer during the period of the illness. Virus isolation in Case 7 was accompanied by the finding of an elevated neutralizing antibody titer (over 1:16) during convalescence, no acute serum specimen being available for comparison.

The prototype of adenoidal-pharyngeal-conjunctival virus, Type 3, was isolated from a human volunteer during studies on the common cold.[2] This virus has also previously been isolated from the eye of a laboratory worker with unilateral conjunctivitis similar to that in Case 2.[3]

Thus, the data in this report, as well as those reported in separate communications,[3,4] suggest that Type 3 virus is capable of causing febrile or nonfebrile rhinitis, pharyngitis and conjunctivitis. However, further clinical and epidemiologic studies are necessary to test this hypothesis.

Table 2. *Evidence for Infection with Adenoidal-Pharyngeal-Conjunctival Virus, Type 3, in 8 Patients with Upper Respiratory Disease.*

Case No.	Age	Isolation of Type 3 Virus			Antibody Titer for Type 3 Virus*			
		Source	Day of Illness	Result	Date	Day of Illness	Complement Fixation	Neutralization
	yr.							
1	2	Nasopharyngeal swab	5	Positive	2/12	3	<8	<4
					3/1	20	128	>16
2	30	Conjunctival swab	3	Positive	2/19	3	16	<4
					3/9	17	16	>64
3	7	—			2/12	−7	<8	<4
					3/1	10	>256	>16
4	28	Nasopharyngeal swab	5	Positive	2/20	2	<8	<4
					3/3	12	>128	>16
5	25	Nasopharyngeal swab	4	Positive	2/12	−8	<8	<4
					3/9	17	>128	>16
6	1	Nasopharyngeal swab	2	Positive	1/26	−27	<8	<4
		Nasopharyngeal swab	8	Negative	3/11	17	>256	>16
7	28	Nasopharyngeal swab	1	Positive	3/15	19	—	>16
8	2	—			2/12	−14	<8	<2
						12	<8	>8

*Expressed as reciprocal of dilution of serum.

Summary

During a two-week period a clinical illness associated with infection with adenoidal-pharyngeal-conjunctival virus, Type 3, occurred in 4 children and 4 adults among the patients and staff of a hospital service. The features of illness in descending order of frequency included pharyngitis, rhinitis, fever, cervical or submandibular lymphadenopathy, conjunctival inflammation and liver tenderness.

References

1. Rowe, W. P., et al. Isolation of cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. *Proc. Soc. Exper. Biol. & Med.* 84:570-573, 1953.
2. Hilleman, M. R., and Werner, J. H. Recovery of new agent from patients with acute respiratory illness. *Proc. Soc. Exper. Biol. & Med.* 85:183-188, 1954.
3. Rowe, W. P., Huebner, R. J., Hartley, J. W., Ward, T. G., and Parrott, R. H. Studies of adenoidal-pharyngeal-conjunctival group of viruses. *Am. J. Hyg.* (in press).
4. Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A. Adenoidal-pharyngeal-conjunctival agents: newly recognized group of common viruses of respiratory system. *New Eng. J. Med.* 251:1077-1086, 1954.

DETERMINATION OF OSMOTIC PRESSURE IN DIABETES INSIPIDUS*

A New Diagnostic Test

LEONARD S. DREIFUS, M.D.,† MARTIN N. FRANK, M.D.,‡ AND SAMUEL BELLET, M.D.§

PHILADELPHIA

THE object of this communication is to report a relatively simple test for the diagnosis of diabetes insipidus: the simultaneous determination of the osmotic pressure of the blood and urine. Diabetes insipidus may be suspected in a patient with polyuria and polydipsia whose urine is consistently of low specific gravity. This syndrome must be differentiated from psychogenic polydipsia with polyuria, "chronic nephritis" and diabetes mellitus. The last two should present no difficulty in differential diagnosis with the aid of ordinary laboratory tests.

Certain procedures that aid in the diagnosis of diabetes insipidus are as follows: alleviation of symptoms after the administration of Pitressin[1]; diuresis and chloruresis in response to an intravenous infusion of hypertonic saline solution[2,3]; the failure of dehydration to increase significantly the specific gravity of the urine; and the failure of inhibition of water diuresis after smoking or administration of nicotine.[4]

The present report emphasizes the value of determinations of osmotic pressure in diabetes insipidus. Because of the specificity and relative simplicity of this technic, we consider it an important addition to the existing diagnostic procedures.

MATERIALS AND METHODS

Four patients with diabetes insipidus served as subjects for this study. These patients manifested the typical clinical picture of this syndrome, and the diagnosis was confirmed in 3 of them by a positive Hickey–Hare test.¶

The osmotic pressure test is performed after water and food have been withheld from the patient for three hours and fifteen minutes. Two hours and forty-five minutes before the beginning of the test, the patient empties his bladder and discards the urine. At three hours a heparinized blood sample is drawn for determination of the osmotic pressure of the blood. At the time of the test the half-hour aliquot of urine is collected for determination of osmotic pressure.

Osmotic pressure of the blood and urine was determined by measurement of the depression of the freezing point with a Beckman type of thermometer, accurate to 0.001°C.[5] The total solute concentration was expressed in milliosmols per liter. It was assumed that the solutes were totally dissociated. The total solute concentration more correctly should be expressed as milliosmols of sodium chloride. One can obtain this value simply by dividing the milliosmols per liter by 2.

In addition sodium and potassium determinations of the serum and urine were performed by the flame photometer technic using a modification of the method of Overman and Davis.[6] Serum and urinary chlorides were measured by the method of Wilson and Ball.[7]

CASE REPORTS

CASE 1. W.C., a 21-year-old man who had had polyuria and polydipsia since the age of 13, suffered a spontaneous pneumothorax in July, 1950, when congenital cystic disease of the lungs was discovered. He was discharged on therapy consisting of Pitressin Tannate in oil, with excellent control of the polydipsia and polyuria. In September, 1952, he had ceased taking Pitressin, and polyuria developed, necessitating hourly urination throughout the night, with an estimated water intake of 12 to 14 liters daily. He was admitted to the hospital of the University of Pennsylvania in February, 1953, because of infectious hepatitis. Physical examination was unremarkable except for jaundice and hepatomegaly. The polyuria and polydipsia were again well controlled with Pitressin Tannate in oil.

CASE 2. W.N., a 42-year-old nurse, was admitted to the Philadelphia General Hospital on May 6, 1951, with a history of weakness, hunger and sweating since 1935. A hypoglycemic state had been diagnosed in 1945, as a result of an abnormal glucose tolerance curve. One week before admission she had noted the sudden onset of thirst and polyuria, with an estimated intake of 6 to 8 liters of fluid daily. Physical examination revealed a well nourished woman. The blood pressure was 150/90, and a Grade 2 blowing systolic murmur was heard over the precordium. The liver edge was palpable 2 fingerbreadths below the right costal margin. The specific gravity of a random urine specimen was 1.002, and 10 hours after the withholding of fluids the urine specific gravity was 1.012. Visual-field examination was negative and x-ray films of the skull were normal. A Hickey–Hare test performed on May 17 was positive for diabetes insipidus. During the infusion of hypertonic saline solution severe thirst, nausea and temperature elevation developed. With the administration of the Pitressin Tannate in oil there was an amelioration of the polyuria and polydipsia, and the specific gravity of the urine rose to 1.022.

CASE 3. R.D., a 59-year-old fireman, was admitted to the neurology ward of the Philadelphia General Hospital on January 5, 1953, with a history of progressive blindness in the right eye and increasing polydipsia and polyuria (approximately 7 or 8 liters of fluid being taken every 24 hours) for 5 months. He also complained of persistent headaches and an episode of vertigo 1 week before admission. Physical examination was negative except for optic atrophy and absence of vision in the right eye. The blood pressure was 144/88. Spinal-fluid examination was negative, and x-ray films of the skull and cerebral arteriography were normal. A blood serologic test for syphilis was negative. The specific gravity of the urine 18 hours after the withholding of fluids was 1.006. On January 26 the Hickey–Hare test was posi-

*From the Division of Cardiology and the Medical Wards, Philadelphia General Hospital, and the Robinette Foundation, University of Pennsylvania School of Medicine.

†Formerly, resident in medicine, Philadelphia General Hospital.

‡Resident in cardiology, Philadelphia General Hospital.

§Professor of clinical cardiology, University of Pennsylvania School of Medicine; director, Division of Cardiology, Philadelphia General Hospital.

¶The Hickey–Hare test[2] involves intravenous infusion of a 3 per cent solution of sodium chloride with simultaneous measurement of urinary output. With normal function of the supraopticohypophyseal tract, the resultant increased increment in serum solute concentration stimulates the osmoreceptors to release antidiuretic hormone and thus to produce antidiuresis. In diabetes insipidus the flow of urine does not decrease, it is only after Pitressin administration that antidiuresis occurs.

tive (Table 1). The cause of the optic atrophy was not determined, and the patient was discharged on a maintenance dose of Pitressin Tannate in oil.

CASE 4.* A.T.B., a 17-year-old married Negress, was admitted to the Temple University Hospital on July 9, 1952, with a history of progressive thirst and polyuria. She had noted these symptoms from an early age and volunteered the information that she "became feverish" if she did not drink large amounts of water. Physical examination was negative. A random sample of urine had a specific gravity of 1.001. The estimated average fluid intake as well as urinary output was 5 or 6 liters daily. The Hickey–Hare test was positive for diabetes insipidus. The Kolmer test was also positive. She received penicillin therapy. The polyuria and polydipsia were well controlled with Pitressin Tannate in oil.

RESULTS

The serum sodium and potassium values and the osmotic-pressure values of the blood and urine before and after Pitressin administration are shown in Table 2. This table and Figure 1 demonstrate that the ratio of osmotic pressure of the urine to that of the blood (U/P)† was found to be less than 1 in all 4 of these uncontrolled patients with diabetes insipidus. The osmotic pressure (U/P) rose to a value greater than 1 in the 3 patients to whom Pitressin was administered. The urinary concentration of sodium and potassium increased in all cases after the administration of Pitressin.

*Reported in detail by Carfagno et al.[8]

†U = concentration in urine; P = concentration in blood. U/P thus refers to a ratio of concentration of a solute in the urine compared to its concentration in the blood. Any osmotically active solute — for example, sodium, potassium or even total solute concentration — may be measured and referred to in this manner.

The typical results of a positive Hickey–Hare test in Case 3 are shown in Table 1 and Figure 2. With the intravenous infusion of 2.5 per cent saline solution the volume of the urine increased from 7.5 cc. to a maximum of 17.7 cc. per minute. The U/P of sodium, potassium, chloride and osmotic pressure remained essentially unchanged. After the intravenous injection of 5 pressor units of Pitressin there was an immediate rise in the U/P of these electrolytes and the osmotic pressure, with a concomitant fall in urinary volume. No increase in the total excretion of sodium, potassium, chloride and total solutes followed the administration of Pitressin (Fig. 2 and Table 1).

TABLE 1. *Total Solutes and Electrolytes During Hickey–Hare Test in Case 3.*

TIME	SODIUM U/P*	URINARY SODIUM	CHLORIDE U/P*	URINARY CHLORIDE	POTASSIUM U/P*	URINARY POTASSIUM	U/P OF TOTAL SOLUTES*	URINARY SOLUTES	URINE
min.		*milliequiv./min.*		*milliequiv./min.*		*milliequiv./min.*		*milliosmols/min.*	*cc./min.*
0	0.106	0.112	0.294	0.211	2.23	0.086	0.403	0.954	7.5
15	0.176	0.344	0.287	0.396	1.41	0.105	0.226	0.925	13.2
30	0.297	0.795	0.438	0.810	1.57	0.141	0.394	2.210	17.7
45	0.352	0.711	0.472	0.725	0.84	0.053	0.422	1.790	13.4
75	2.440	0.740	1.220	0.684	4.57	0.133	1.230	2.050	5.1

*Ratio of concentration in urine to that in blood.

The failure of a significant change of the U/P of sodium, potassium chloride and osmotic pressure is the response expected with the Hickey–Hare test in a patient with diabetes insipidus. This response indicates an inability of the tubules to concentrate the urine and probably represents a deficiency of liberation of antidiuretic hormone after the infusion of hypertonic saline solution. The marked increase of urinary electrolyte concentration that followed the injection of Pitressin demonstrated the ability of the tubule cells to perform their function when an exogenous hormone was present.

TABLE 2. *Total Solutes and Electrolytes before and after Pitressin.*

CASE NO.	EXPERIMENTAL CONDITION	SERUM SODIUM	SERUM POTASSIUM	SERUM SOLUTES	URINARY SODIUM	URINARY POTASSIUM	URINARY SOLUTES	SOLUTE U/P
		milliequiv./liter	*milliequiv./liter*	*milliosmols/liter*	*milliequiv./liter*	*milliequiv./liter*	*milliosmols/liter*	
1	Control	141	5.52	344	25.1	44.4	285	0.84
	Pitressin	137	5.12	327	50.0	86.8	514	1.57
2	Control	146	4.98	324	16.2	14.4	153	0.48
	Pitressin	145	4.48	326	102.4	74.1	893	2.74
3	Control	156	4.93	336	68.0	8.0	140	0.42
	Pitressin	150	5.56	331	145.0	25.4	402	1.22
4	Control	142	4.26	312	12.4	9.5	117	0.375

DISCUSSION

Diabetes insipidus is characterized by an inability of the kidney to elaborate a urine that is hypertonic to the blood,[9] absence of antidiuretic hormone in the

blood and urine,[10] failure of antidiuresis after the intracarotid infusion of hypertonic solutions[11] and immediate diuresis and ability of the distal tubular cells of the kidney to concentrate urine when exogenous Pitressin is supplied.[1]

Verney[11] has postulated that the release of antidiuretic hormone is mediated by the osmoreceptors of the neurohypophyseal tract in response to an increase in the effective osmotic pressure of the blood. This mechanism is perverted in conditions characterized by edema, such as congestive heart failure, cirrhosis of the liver and renal disease, all of which are associated with increased titers of antidiuretic hormone in the blood and urine when edema is present.[12]

Several investigators[8,13,14] have found that the injection of Pitressin does not cause a change in the total output of sodium and chloride nor does it alter the glomerular filtration rate in normal subjects or those with diabetes insipidus.

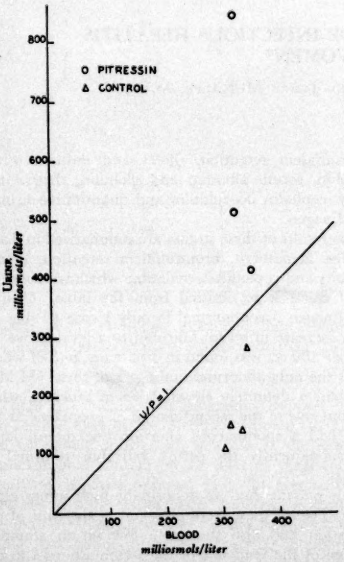


FIGURE 1. *U/P Solute before and after the Administration of Pitressin.*

During the period of salt loading in Case 3 (Table 1) there was an increase in urinary volume (7.5 cc. to 17.7 cc. per minute), with a corresponding increase in excretion of sodium, potassium, chloride and total solute. This is the anticipated response in patients with diabetes insipidus and illustrates the increased urinary volume that follows an increased solute load. After the intravenous injection of Pitressin there was no change in the total excretion of sodium potassium, chloride and total solutes despite their increased concentration in the urine, indicating that Pitressin acts solely by causing reabsorption of water at the distal renal tubule cells and that it had no effect on the tubular excretion of sodium, chloride or potassium.

These results demonstrate that total solute concentration of the urine is always less than that of the blood in the uncontrolled patient with diabetes insipidus. Total solute U/P was always greater in such cases than in water-loaded patients with diabetes mellitus, chronic glomerulonephritis, chronic pyelonephritis, Kimmelstiel–Wilson's disease and normal subjects.

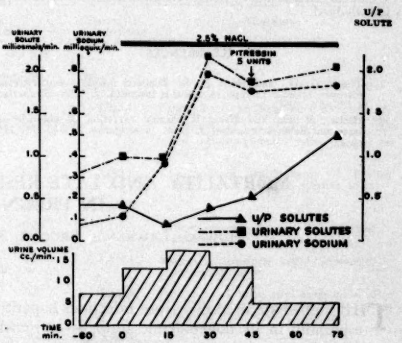


FIGURE 2. *Hickey–Hare Test in Case 3.*

The determination of total solutes of the blood and urine was performed three hours after the withholding of water and food because Baldes and Smirk[15] have shown that the urine is maximally diluted forty to sixty minutes after water loading and the prehydration concentration is reached within three hours.

A patient with psychogenic polydipsia and polyuria will have a greater total solute concentration of urine than blood at three hours, and psychogenic polyuria may thus be differentiated from diabetes insipidus.

The fact that a patient with diabetes insipidus always has a urine that is hypotonic to the blood indicates the basis for this diagnostic test — that is, the simultaneous determinations of the osmotic pressure of the blood and urine.

SUMMARY

Total solutes and electrolytes in the blood and urine were determined in 4 cases of diabetes insipidus. The ratio of concentration of total solute in urine to that in blood was less than 1 in the uncontrolled state, and greater than 1 after the administration of Pitressin.

There was an increase in the urinary excretion of sodium potassium, chloride and total solute when 1 patient was infused with 2.5 per cent of sodium

chloride solution. With the intravenous administration of Pitressin the urinary excretion of these solutes remained relatively constant, indicating that the effect of Pitressin is on the tubular reabsorption of water.

The basis for this simple test in the diagnosis of diabetes insipidus is discussed.

We are indebted to Drs. John Urbach and J. Randolph Sharpsteen for reviewing the manuscript and to Dr. Charles Shuman, of Temple University, and Drs. Francis Wood and Robert Dowben, of the University of Pennsylvania, for permission to perform these studies on their patients. The technical assistance of Mrs. Renate Medved is also acknowledged.

References

1. Thorn, G. W., and Stern, K. E. Diabetes insipidus and Pitressin: Pitressin tannate therapy in diabetes insipidus. *J. Clin. Endocrinol.* 1:680-687, 1941.
2. Hickey, R. C., and Hare, K. Renal excretion of chloride and water in diabetes insipidus. *J. Clin. Investigation* 23:768-775, 1944.
3. Hare, R. S., Hare, K., and Phillips, D. M. Renal excretion of chloride by normal and by diabetes insipidus dog. *Am. J. Physiol.* 142:334-348, 1943.
4. Burn, J. H., Truelove, L. H., and Burn, I. Antidiuretic action of nicotine and of smoking. *Brit. M. J.* 1:403-406, 1945.
5. Sharpsteen, J. R. Personal communication.
6. Overman, R. R., and Davis, A. K. Application of flame photometry to sodium and potassium determinations in biological fluids. *J. Biol. Chem.* 168:641-649, 1947.
7. Wilson, D. W., and Ball, E. G. Study of estimation of chloride in blood and serum. *J. Biol. Chem.* 79:221-227, 1928.
8. Carfagno, S. C., Durant, T. M., and Shuman, C. R. Diabetes insipidus in pregnancy. *Arch. Int. Med.* 92:542-553, 1953.
9. Leaf, A., Manby, A. R., Rasmussen, H., and Maranco, J. P. Some hormonal aspects of water excretion in man. *J. Clin. Investigation* 31:914-927, 1952.
10. Gilman, A., and Goodman, L. Effect of pituitrin injection in rabbits on serum osmotic pressure and blood picture. *Proc. Soc. Exper. Biol. & Med.* 33:238-240, 1935.
11. Verney, E. B. Antidiuretic hormone and factors which determine its release. *Proc. Roy. Soc. London* 135:25-106, 1947.
12. Dochios, M., and Dreifus, L. S. Antidiuretic hormone studies in patients presenting edema. *Am. J. M. Sc.* 222:538-543, 1951.
13. Sinclair-Smith, B. C., et al. Effects of posterior pituitary extract and smoking on water, sodium and chloride excretion in normal subjects and in patients with congestive cardiac failure. *Bull. Johns Hopkins Hosp.* 87:221-234, 1950.
14. Dicker, S. E., and Heller, H. Renal action of posterior pituitary extract and its fractions as analyzed by clearance experiments on rats. *J. Physiol.* 104:353-360, 1946.
15. Baldes, E. J., and Smirk, F. H. Effect of water drinking, mineral starvation and salt administration on total osmotic pressure of blood in man, chiefly in relation to problems of water absorption and water diuresis. *J. Physiol.* 82:62-74, 1934.

MORTALITY AND LATE RESULTS OF INFECTIOUS HEPATITIS IN PREGNANT WOMEN*

Howard Lawrence Frucht, M.D.,† and James Metcalfe, M.D.‡

BOSTON

THE immediate mortality from infectious hepatitis, especially in its nonepidemic form, is extremely low. Previous work has suggested a higher mortality in pregnant women, at least in areas where undernutrition is common.

It was the purpose of the study reported here to investigate the immediate mortality of infectious hepatitis in pregnant women and also to evaluate liver function a year or more after the acute episode in women who survived.

All cases diagnosed as nonobstructive jaundice at the Boston Lying-in Hospital in the past eighteen years were reviewed to select patients for this study. No case occurring more recently than twelve months was included. Only patients who suffered an acute febrile illness clinically compatible with the disease now called infectious hepatitis were accepted in the study. In every case obstructive jaundice had been ruled out, and there was no evidence of toxemia of pregnancy. Seventeen patients were found who met these criteria; 2 of these had died of the acute disease.

Of the 15 who survived pregnancy and infectious hepatitis, 12 were located, 11 of whom returned for follow-up study. This consisted of a medical history, careful examination for physical signs of liver disease and the following laboratory tests: hematocrit, bromsulfalein retention, direct and indirect serum bilirubin, serum albumin and globulin, thymol turbidity, cephalin flocculation and quantitative urinary urobilinogen.

The results of these studies are summarized in Table 1. The hematocrit, bromsulfalein retention, thymol turbidity and cephalin flocculation, which were normal in all cases, were omitted from the table. Urinary urobilinogen was abnormal in only 1 case (Table 1).

An increase in serum bilirubin to a level above 1.0 mg. per 100 cc. was found in 5 patients, in 3 of whom it was the only abnormal finding; 1 of these (M.M.), who had a definitely elevated serum bilirubin when seen but was in the second month of pregnancy at the time, had a spontaneous abortion one month later, and subsequently the serum bilirubin returned to normal.

Four patients had an abnormally high serum globulin.§ Two of these were pregnant at the time of examination and also showed a low serum albumin. Because of the tendency of the serum albumin to decrease and the serum globulin to rise in normal pregnancy[1] the significance of these findings is not clear.

Liver size is given as fingerbreadths below the right costal margin in the midclavicular line. In all cases the upper edge of liver dullness was percussed in an attempt to rule out downward displacement as the cause of palpability. In no case was the upper border of liver dullness below the fifth intercostal space. In 6 women the liver edge could not be felt, and 3 of

*From the laboratory of Dr. C. Sidney Burwell at the Boston Lying-in Hospital, the Department of Medicine, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.
Aided by a grant from the United States Public Health Service, Cardiovascular Study Section.

†Formerly, assistant resident in medicine, Peter Bent Brigham Hospital.

‡Instructor in medicine, Harvard Medical School; associate physician, Boston Lying-in Hospital; junior associate in medicine, Peter Bent Brigham Hospital. (This work was done during the tenure of an Established Investigatorship of the American Heart Association.)

§The upper limit of normal for nonpregnant patients in our laboratory is 3.5 gm./100 cc. In pregnant women the upper limit of normal rises to 4.0 gm./100 cc.

these had an increased serum bilirubin. In 2 cases the liver edge was felt 2 fingerbreadths below the right costal margin, and there was confirmatory evidence of liver disease by laboratory examination. In 3 patients the edge was only 1 fingerbreadth below the right costal margin; 1 of these had coexistent palpable splenomegaly and a decrease in serum albumin.

There was no apparent correlation between severity of the acute disease and evidence of chronic impairment of liver function.

could expect an increased severity and mortality from liver disease occurring during this period. Dill[4] has reviewed the literature and supported with additional cases the finding of an increased incidence of acute yellow atrophy in pregnancy. Zondek and Bromberg,[5] who followed a group of pregnant women in an epidemic of infectious hepatitis in Jerusalem, remarked on the increased mortality in pregnant women (17 per cent of 29 patients studied) but emphasized the role of malnutrition as a factor. In our

TABLE 1. *Follow-up Studies of Patients Recovering from Infectious Hepatitis in Pregnancy.*

PATIENT	INTERVAL SINCE INFECTIOUS HEPATITIS	TRIMESTER IN WHICH HEPATITIS CONTRACTED	HEPATOMEGALY	SPLENOMEGALY	SERUM BILIRUBIN		SERUM ALBUMIN-GLOBULIN RATIO	COMMENT
					TOTAL	AT 1 MIN.		
	yr.		*finger-breadths*	*finger-breadths*	*mg./100 cc.*	*mg./100 cc.*	*gm./100 cc.*	
M.M.	8	3d	0	0	3.2	0.9	3.9/3.1	Patient 2 mo. pregnant when re-examined; after abortion bilirubin fell to 0.5 mg. per 100 cc. total & 0.3 mg. direct, and albumin-globulin ratio changed to 4.9/2.5.
R.H.	9	3d	2	0	1.8	0.4	3.6/3.8	2-hr. urinary urobilinogen 3.2 Ehrlich units (normal, 0.5-1.5 Ehrlich units)
O.Te.	2	3d	0	0	1.7	0.3	4.8/2.8	——
O.To.	9	3d	0	0	1.5	0.5	4.2/3.0	Patient subsequently had 2 uneventful pregnancies
M.T.	2	3d	2	0	1.2	0.8	4.8/3.1	Patient subsequently had 1 uneventful pregnancy
R.G.	3	3d	1	0	1.0	0.3	3.5/3.9	Patient had 2 uneventful pregnancies after infectious hepatitis & was 5 mo. pregnant at time of re-examination
M.Bl.	1	3d	1	2	0.6	0.4	3.4/3.0	——
M.Br.	3	3d	1	0	0.9	0.5	3.3/3.9	Patient 3 mo. pregnant when re-examined
J.V.	16	3d	0	0	0.8	0.4	4.2/4.0	——
M.G.	18	3d	0	0	0.9	0.2	4.0/3.4	——
D.C.	4	1st	0	0	0.9	0.3	4.2/3.4	——

Thus, of the 11 women examined, only 2 were free of clinical and laboratory evidence of liver disease.

DISCUSSION

There is evidence that pregnancy imposes a burden on the liver of the pregnant woman. Kosterlitz and Campbell[2] showed an increase in the desoxyribonucleic acid content of the liver of pregnant rats, signifying, in their opinion, that "in pregnancy the liver has to fulfill its metabolic functions not only for the maternal body but also for the foetuses." Cross[3] found that minor infections occurring in pregnancy caused an abnormal bromsulfalein retention, apparently showing a decreased hepatic reserve. In our series 1 patient, who had had infectious hepatitis in a previous pregnancy, was found to have an increase in serum bilirubin during a subsequent pregnancy; the bilirubin fell to normal after a spontaneous abortion, suggesting a decreased hepatic reserve. Furthermore, our 2 cases with slight hepatomegaly and reversal of the albumin-globulin ratio during pregnancy may also represent liver damage detectable only under the burden of pregnancy.

If, then, the liver is burdened by pregnancy, one

series 2 women died of acute yellow atrophy out of the 17 seen with infectious hepatitis during pregnancy. Malnutrition did not seem to be a factor in these deaths.

Since infectious hepatitis does lead to chronic liver disease in some cases[6] and since pregnancy appears to place a load on the liver, we have attempted to determine whether infectious hepatitis occurring in pregnancy causes an increase in chronic liver disease.

The frequency of chronic liver disease after infectious hepatitis in nonpregnant patients is not clear. Jones[7] states that chronic hepatic impairment evidenced by continued elevation of the serum bilirubin is not rare. Kunkel, Labby and Hoagland,[8] following 350 young men with acute hepatitis, found 13 with either clinical or chemical evidence of persistent disease after a year. A more recent study by Zieve et al.[9] of 367 cases of viral hepatitis evaluated four to six years after the acute illness showed no increased prevalence of hepatocellular disease as compared with a control group. Altschule and Gilligan[10] studied 36 cases one to twenty-nine years after acute hepatitis and found a serum bilirubin above 1.0 mg. per 100 cc. in 6. As in the present study an elevated serum

bilirubin was the most frequent abnormality. Similarly, Kunkel, Labby and Hoagland[8] reported an elevation of serum bilirubin to be the most frequent abnormality in their cases with evidence of chronic liver disease a year after an acute attack of hepatitis.

Of our 11 patients, 5 had a serum bilirubin higher than 1.0 mg. per 100 cc. An additional 3 showed elevation of serum globulin, which in 2 cases was perhaps due to pregnancy, and another demonstrated hepatosplenomegaly and a low serum albumin. Only 2 had entirely normal clinical and laboratory findings. The frequency of chronic hepatic disease in this series was therefore higher than one would expect after infectious hepatitis in nonpregnant patients according to the studies reviewed above.

Of interest in our study is the fact that 15 of 17 cases occurred in the last trimester of pregnancy. This weighting is corroborated by Zondek and Bromberg,[5] who found 19 of 29 patients in the second half of gestation, suggesting either that infectious hepatitis is more apt to be overt and clinically recognizable in the second half of pregnancy or that pregnant women are more susceptible to infectious hepatitis in the latter months of pregnancy.

The results of this study are applicable only to infectious hepatitis occurring in the last trimester. The acute severity of the disease at that period of pregnancy has been emphasized by Zondek and Bromberg[5] and Dill[4] and is supported by our series, in which the only 2 deaths occurred in the last trimester.

It should be emphasized that none of our patients had symptoms of liver disease at the time of follow-up examination. Thus, although we believe that persistent liver damage is frequent, it may not be progressive. It is possible that the abnormalities found are only indicative of damage incurred at the time of the infectious hepatitis. There is no evidence of a continuing process that will eventually lead to clinical disability, but avoidance of further liver damage in these patients is important.

Summary

Eleven women who had had infectious hepatitis during pregnancy one to eighteen years previously were investigated for evidence of liver damage. Only 2 were free of clinical and laboratory evidence of liver disease.

This small series of cases suggests that infectious hepatitis, when it occurs in the last trimester of pregnancy, carries a higher mortality and a greater tendency to chronic liver damage than when it occurs in the nonpregnant patient.

References

1. Macy, I. G., and Mack, H. C. *Physiological Changes in Plasma Proteins Characteristic of Human Reproduction*. 170 pp. Detroit, Michigan: Children's Fund of Michigan.
2. Kosteritz, H. W., and Campbell, R. M. Composition and structure of liver cell in pregnancy. *Nature* (London) **160**:676, 1947.
3. Cross, R. C. Study of various liver function tests in normal pregnancy. *Am. J. Obst. & Gynec.* **18**:800-807, 1929.
4. Dill, L. V. Acute yellow atrophy of liver associated with pregnancy: review of literature and six cases. *Obst. & Gynec. Surv.* **5**: 139-158, 1950.
5. Zondek, B., and Bromberg, Y. M. Infectious hepatitis in pregnancy. *J. Mt. Sinai Hosp.* **14**:222-243, 1947.
6. Kunkel, H. G., and Labby, D. H. Chronic liver disease following infectious hepatitis. II. Cirrhosis of liver. *Ann. Int. Med.* **32**:433-450, 1950.
7. Jones, C. M. Personal communication.
8. Kunkel, H. G., Labby, D. H., and Hoagland, C. L. Chronic liver disease following infectious hepatitis. I. Abnormal convalescence from initial attack. *Ann. Int. Med.* **27**:202-219, 1947.
9. Zieve, L., Hill, E., Nesbitt, S., and Zieve, B. Incidence of residuals of viral hepatitis. *Gastroenterology* **25**:495-531, 1953.
10. Altschule, M. D., and Gilligan, D. R. Chronic latent hepatitis following catarrhal jaundice. *New Eng. J. Med.* **231**:313-317, 1944.

MEDICAL PROGRESS

RADIOLOGIC EXAMINATION OF THE GASTROINTESTINAL TRACT (Concluded)

JOHN E. GARY, M.D.,* AND RICHARD SCHATZKI, M.D.†

BOSTON

Duodenum

Duodenal Ulcer

Templeton[51] reiterates the truism that the only basis for a diagnosis of active ulcer is demonstration of a crater. He found that the deformity associated with ulcer appears shortly after the onset of symptoms and shows little change thereafter, regardless of healing or recurrence of the crater. Some ulcers heal without leaving a deformity. He favors periodic x-ray examination as a means of judging the efficacy of treatment.

*Assistant in radiology, Harvard Medical School; associate radiologist, Mount Auburn Hospital, Cambridge, Massachusetts.

†Instructor in radiology, Harvard Medical School; radiologist-in-chief, Mount Auburn Hospital, Cambridge, Massachusetts.

Ettinger[52] presented cases of duodenal ulcer in which there was extensive scarring with a resultant wide, gaping pylorus. This made it difficult to locate the pylorus accurately and therefore also difficult to decide whether the ulcer was on the gastric or the duodenal side of the pylorus.

Ulcers in the duodenum distal to the bulb are not common but, when present, frequently produce episodes of massive bleeding. Ball, Segal and Golden[53] stress the importance of films taken in an almost lateral projection to detect these ulcers, which may otherwise be hidden by the barium-filled bulb. An incisura opposite the crater was a constant finding in their cases. The search for peptic ulcer should not stop at the duodenal bulb.

Hyperplasia of Brunner's glands[54,55] and carcinoid tumors[56] have been described, causing polypoid masses in the duodenal bulb.

Small Intestine

Segmental Study

Friedman and Rigler[57] describe a triple lumen tube with which a segment of the small intestine may be isolated between two inflated balloons and studied with barium or barium and air. The barium can be removed after the study is completed. If an obstruction is encountered, barium is injected beyond the distal balloon and the obstructing lesion limits the amount of small intestine filled. The method is particularly recommended to search for a bleeding source when conventional studies fail.

The source of bleeding from the jejunum or ileum was identified in 43 of 51 cases reported by Dedick and Collins[58] in which the small intestine had been examined preoperatively. Few of these required intubation studies since the lesion could be seen on serial films made after ingestion of barium. Cancer, regional enteritis and carcinoid were the three most common lesions seen, in that order. Evidence of obstruction is, of course, a contraindication to the administration of barium by mouth.

Periumbilical Pain and Intermittent Intussusception in Childhood

A problem seen frequently by the radiologist is the young patient, more often a girl and under ten years of age, who complains of recurrent attacks of periumbilical pain and in whom there are few or no objective abnormalities. Teitelbaum and Arenson[59] observed short intussuscepted segments of small intestine in 4 such cases on films made up to two hours after a barium meal; these segments sometimes disappeared spontaneously during the course of the examination, and sometimes varied in location in the same patient on different films. A fifth patient was operated on, and the same phenomenon was seen by the surgeon. A study of a number of such children during an attack of pain seems indicated before the authors' conclusions are accepted, although the intussuscepted segments described are not uncommonly seen in cases with similar histories.

Barium-Enema Reduction of Intussusception

Although it has been common practice in the Scandinavian countries to reduce intussusceptions in the ileocecal area in children by means of the barium enema, the method has only recently found champions in this country. In a monograph on the subject, Hellmer,[60] of Lund, describes successful reduction in 130 out of 162 cases between 1933 and 1947, with no deaths. In the remaining 32 cases, which could not be reduced in this manner and were treated surgically, 9 patients died, but only 2 had a history of less than twenty-four hours' duration.

Ravitch and McCune,[61] at the Johns Hopkins Hospital, have used the barium enema to reduce intussusception routinely, followed by surgery only if complete reduction is not demonstrated by the barium enema. Of 32 cases 22 were reduced by barium enema. There were no deaths, and the authors cite less ileus, less fever, lack of mechanical obstruction developing from adhesions at a later date and a greatly shortened hospital stay as additional advantages in comparison to surgical treatment. They place the enema can 90 cm. above the patient, and do not consider reduction complete unless there is a free flow of barium into the ileum. If reduction does not occur after several moments of hydrostatic pressure, the patient is allowed to empty his colon, and the procedure is repeated.

The Children's Hospital in Pittsburgh has adopted a similar policy,[62] with a report of 22 reductions in 27 cases seen. One death with convulsions occurred twenty-four hours after reduction, but autopsy showed the reduction to be complete, with no gangrene.

In none of the series mentioned above has a limit been set between onset of symptoms and time of attempt at reduction by barium enema. All authors claim that it is impossible to reduce bowel that is gangrenous.

Idiopathic Purpura

Abnormalities seen in the small intestine consist of markedly irregular mucosa and dilated loops, as well as segments of constriction.[63-65] These are due to foci of hemorrhage in the intestinal wall and result in diarrhea, colicky pain, melena and sometimes intussusception.

Perforation

Rupture of the small intestine rarely causes free air beneath the diaphragm, especially if the perforation is due to acute trauma. Of 19 cases of rupture from nonpenetrating abdominal injuries reported by Jacobson and Carter[66] only 2 showed pneumoperitoneum. Many patients had no x-ray signs of injury despite gross perforation and peritonitis.

Perforation through the posterior wall of the duodenum may cause air to dissect along the crus of the diaphragm and to be visible under the medial margin of the left leaf of the diaphragm, or around the left kidney.[67] Escape of fluid retroperitoneally results in inflammation and obliteration of the psoas-muscle shadow.

Ileus

The radiologist is frequently called upon to help differentiate mechanical and paralytic ileus. A monograph stressing this problem[68] should be consulted in the original. In some cases the actual cause of mechanical obstruction can be seen — volvulus, internal or external hernias or gallstone ileus, or

when a tumor of the bowel is outlined by air within the bowel. Mesenteric thrombosis may be suspected in some cases in which rapid distention of the small intestine occurs, and in which the mucosal pattern is either lost or shows thickened folds with an irregular serrated bowel contour.[69,70]

Too frequently, however, we personally find it impossible to differentiate mechanical and paralytic ileus from the films alone.

Cantor[71] suggests that an ounce or two of barium be injected through the intestinal decompression tube before it is removed, when from clinical evidence it appears that the need for it has passed. The barium is then followed for the next twenty-four hours, to make sure that obstruction is no longer present. This supposedly prevents the necessity of reinsertion.

Regional Enteritis

Progression of this disease to involvement of the jejunum is an unfavorable prognostic sign according to Janus.[72] A review of 71 cases of Marshak and Wolf[73] showed 12 involving the jejunum. The authors divided the disease into nonstenotic and stenotic stages, and all cases in which the jejunum was involved were in the latter stage.

Disorders of Motor Physiology

Some new aspects of the so-called deficiency pattern in the small intestine have been reported. Anderson et al.[74] discovered that stabilized suspensions of barium prevented the flocculation seen in celiac disease with ordinary barium mixtures. During active celiac disease, abnormally dilated loops of small intestine were found that disappeared during remission, only to recur during subsequent relapses.

Segmentation of a barium meal in the small intestine can be produced in normal persons by addition to the barium solution of hypertonic solutions such as 40 per cent glucose, 80 cc. of 1 per cent lactic acid, 6 gm. of hydrolized olive oil or fecal fat obtained from patients with sprue.[75] Ingestion of allergens in a sensitized patient will cause similar changes.[76]

Meckel's Diverticulum

Although rarely identified, a huge diverticulum has been described preoperatively that, on the plain film of the abdomen, was seen as a large sac filled with air and fluid.[77]

Colon

Methods of Examination

The last decade has seen a definite improvement in the roentgenologic examination of the colon. Improvements have been due not so much to any complete innovation as to more accurate and more conscientious uses of old technics. The improvement is particularly striking in the demonstration of small tumors of the colon. The addition of tannic acid to the barium mixture has become widely used[78]: 10 gm. of fluffy tannic acid powder and 1 liter of barium solution has been recommended as an amount that will cause more complete evacuation and better demonstration of the mucosal pattern after evacuation.[79] We have seen occasional fainting caused by the 1 per cent solution of tannic acid and believe that a 0.3 to 0.5 per cent solution is sufficient for diagnosis. We have not seen any ill effects from such a solution of tannic acid. In contrast to other statements in the literature, we have not found such a solution to be a handicap in air studies of the colon.

Double-contrast study of the colon with barium mixtures and air has become considerably more popular in recent years. First proposed by Fischer in 1923, it was introduced in this country by Weber. The increased interest in recent years is primarily due to the enthusiastic and careful work of Stevenson[80,81] and his group, who have proved the advantages of air studies, particularly in the demonstration of small tumors. These authors, like many others, believe that it is necessary to use special barium preparations that are less apt to sediment. Such finely dispersed barium powders are on the market. Their greater viscosity, however, causes additional technical problems. These and other difficulties of the examination are being helped by a three-way valve system that allows barium solution or air to be injected alternately and aspirated at will and thus permits one to vary the amount of filling at any time to obtain a regular and an air-contrast enema at one sitting with greater ease.[82]

The use of thinner barium mixtures and of higher kilovoltages (up to 130) makes the barium-filled colon more translucent, and intraluminal tumors can be seen through the barium column.[83,84] The necessity of various positions and projections for the demonstration of lesions, particularly in the sigmoid, has been convincingly stressed in recent papers.[85,86]

Careful fluoroscopic examination and adequately exposed spot films in varying degrees of obliquity remain basic requisites, particularly for the study of the sigmoid colon. Repeat examinations are being done with regularity when the colon is not absolutely clean for the initial examination.

The knowledge that it is possible to demonstrate tumors of the colon 5 mm. in diameter has considerably increased the responsibility of the radiologist. It forces him to demonstrate the whole inside of the organ with various degrees of filling. This has made the examination of the colon more complicated and more protracted, but quite rewarding. The number of tiny asymptomatic malignant tumors discovered at routine examination is striking. Considering the high cure rate of such tumors of the colon, if discovered early, the necessity for painstaking examination, with the life-saving effect in such cases, cannot be overemphasized. The clinical results of the improvement in radiologic technic can be clearly seen

in the increasing number of discussions at surgical conventions about the proper way of handling patients who have such minute lesions, either single or multiple.

Deformity in Anastomosis

Deformity in contour at the site of end-to-end anastomosis after resection for cancer may be difficult to differentiate from recurrent or persisting tumor. Sharpe and Golden[87] reviewed 42 cases in which examination had been done after anterior resection, and found only 3 in which no deformity was present at the line of anastomosis. The constriction was shorter than 1 cm. in 27 and longer in 12. The constriction was concentric in 35 and unilateral in 4.

Recurrence at the line of resection is most frequent about two years after operation. If all such patients were to have a follow-up barium-enema examination within the first six months, before deformity is likely to be due to tumor, it would be easier to decide whether a deformity seen at a later date was caused by tumor.

The Appendix

Mucocele of the appendix causes a mobile, sharply circumscribed mass that indents and cannot be separated from the cecum. It may show peripheral calcification. The appendix does not fill when a barium enema is given.[88]

Fecaliths in the appendix mean obstruction in the lumen proximal to the stone, and several reports[89-91] stress the fact that surgery is indicated when they are demonstrated. They may show laminated calcification, and should always be searched for when films of an acute abdomen are taken. If they are seen an appendiceal abscess should be suspected.

Volvulus of the Cecum

About 10 per cent of the population has a mesocecum long enough to allow volvulus to occur.[92] The patient presents an acutely painful abdomen, and in about half the cases there is a history of a previous similar attack. Half of 100 cases collected from the literature[93] were in patients twenty to forty-five years of age. Films of the abdomen show a greatly dilated cecum, which is most often inverted and in the left upper quadrant. Varying degrees of dilatation of the ascending colon and ileum are present, and there is no distention of the left half of the colon. A normal cecal shadow is not seen in the right lower quadrant, and barium-enema study shows the twisted mucosa at the site of volvulus.

Volvulus of the Sigmoid

The x-ray changes on the plain films of the abdomen may be diagnostic.[94-96] A long, dilated, U-shaped loop of the colon is seen, with both limbs of the U of the same caliber, and a fluid level is observed in each limb in films taken with the patient in the upright position. Moderate distention of the colon proximal to this loop is present, being greater if the ileocecal valve is competent. Barium-enema examination shows a typical "bird's bill" termination of the barium column caused by the twisted colon wall.

Ulcerative Colitis

Early in the disease the colon may appear normal on barium-enema study, even though characteristic changes are present on sigmoidoscopy. The first x-ray change on which the diagnosis can be based is a fine, serrated margin, usually seen in the sigmoid and sometimes visible only on the postevacuation film.[97]

Despite apparent marked scarring, an occasional case shows complete return to normal, both clinically and by x-ray study.[98] On the other hand, carcinoma, usually of a highly anaplastic nature, eventually develops in about 5 per cent of cases; this was the frequency in 2000 cases followed for as long as twenty years at the Mayo Clinic.[99]

Hirschsprung's Disease

The pull-through operation devised by Swenson[100] has revolutionized the attack on this disease.

The x-ray diagnosis can be made only if there is a greatly narrowed segment of rectosigmoid with a considerably dilated colon above. Fluoroscopy in the oblique position should be done, and the barium stopped when it enters the dilated portion of the bowel above the narrowed segment. The postevacuation film shows inability to empty the colon.[101] Death has occurred from water intoxication when the entire bowel was filled with barium-water solution.[102] One can avoid this by the use of saline solution as a diluent, or better still, by limiting the examination to the rectosigmoid.

Hemangiomatous Tumors

These lesions may be diagnosed preoperatively when multiple punctate areas of calcification are seen grouped about a narrowed segment of colon that otherwise looks like cancer.[103]

Biliary System

Plain Film of the Abdomen

Evidence of disease of the biliary system — particularly calcified gallstones — may be identified on the plain film of the abdomen.

Air in the bile ducts is usually due to an internal biliary fistula; in a review of over 800 reported cases, Waggoner and LeMone[104] found that 90 per cent were due to erosion of a gallstone through the gallbladder wall into the gastrointestinal tract. Only 6 per cent were caused by perforation of a duodenal ulcer through the wall of the common duct.

Acute gaseous cholecystitis is rare and is due to

infection of the gall bladder by a gas-forming organism.[105-107] Air may be seen both within the lumen of the gall bladder and in its wall, as well as occasionally in the biliary tree. These patients frequently have diabetes.

Stellate gas shadows may be seen within gallstones. These gas-filled fissures are unique in appearance and usually form within stones that contain insufficient calcium to be seen.[108]

Cholecystography

Cholecystography, for many years one of the most reliable radiologic examinations,[109-111] has been further improved by the introduction of new contrast mediums. Because of a higher iodine content these new drugs, of which Telepaque is the most commonly used, cast denser gall-bladder shadows and, in addition, have fewer unpleasant side effects.[112] The obliteration of small stones by the densely opacified gall bladder can be avoided either by spot films taken in the upright position with compression or by films taken in the right lateral decubitus position.[113]

In the absence of jaundice or severe liver damage nonfilling of the gall bladder with the newer drugs has become a very reliable indicator of gall-bladder disease — most often of cholelithiasis. Congenital absence of the gall bladder[114] or a double gall bladder with disease involving only one[115] are rare conditions in which positive and negative errors are unavoidable. Cases of acute pancreatitis in which the gall bladder fails to fill but on later examination was normal have been reported.[116] Liver-function tests were negative in these cases, and no cause for this phenomenon is known.

The major bile ducts are frequently seen with the newer contrast mediums.

Cholangiography

Operative and postoperative cholangiography. Cholangiograms during biliary-tract surgery are taken with ever-increasing frequency as reports on the advantages of the procedure accumulate. Mixter, Hermanson and Segel[117] found that the surgeon, in probing the common duct, missed 1 case of stones in 7, and most of these were seen on the cholangiograms. By the use of cholangiograms the authors were able to reduce the frequency of negative common-duct explorations from 45 to 31 per cent, with a consequent reduction in mortality and morbidity.

Hight and Lingley[118] recommend it for all operations on the extrahepatic biliary tree unless it is apparent that disease is limited to the gall bladder. Technic is important if satisfactory films are to be obtained. Grid cassettes or a Bucky diaphragm is essential, and an x-ray machine capable of 150-200 ma is desirable. For details of the procedure the studies referred to above[117,118] should be consulted.

Postoperative cholangiograms should be taken in all cases before the T tube is removed, even if they have been taken during the operation. Hicken et al.[119] found additional stones that had been missed at operation in 12 per cent of cases in which stones had been found in common-duct explorations.

Rigler and Mixer,[120] have a good explanation for the fever that frequently follows cholangiography. They saw filling of kidney calyxes after cholangiography in 8 of 460 cases studied. All 8 patients had common-duct obstruction, and no dye entered the duodenum. From this the authors deduced that dye enters the blood stream from the biliary tree and thought that bacteria or bile might act in the same way. Radioactive phosphorus was injected through the T tube and found in the blood stream within five minutes. Bile or bacteria forced into the blood stream seems the most likely explanation for the pyrexia that sometimes occurs after cholangiography. The frequency of pain and fever can be reduced by slow injection under low pressure.

Peroral cholangiography. Twiss et al.[121] and Shehadi[122] have been able to demonstrate the major biliary ducts by means of Telepaque, often using 6 gm. of the drug for more intense shadows. The former give paregoric to lessen spillage of the dye through the sphincter of Oddi. The duct system is best seen in films made ten to thirty minutes after a fatty meal.

Intravenous cholangiography. An immensely important step forward has been the introduction of a new intravenously administered, iodine-containing contrast medium. First used in Germany under the name of Biligrafin,[123] it is now available in the United States under the name of Cholografin.[124-126] The concentration of the drug in the liver bile is so great that it does not need further concentration by the gall bladder to cast a shadow. It is possible to see the bile ducts before the gall bladder is seen. It has thus become possible for the first time to study the filling mechanism of the gall bladder accurately. More important than these physiologic studies is the fact that the common duct and the larger hepatic ducts can now be almost routinely demonstrated without incision of the abdomen. Preoperative demonstration of stones in the common duct, regardless of whether or not stones are present in the gall bladder, is obviously of interest to the surgeon. The greatest practical use for this new drug has been the demonstration — until recently, impossible for all practical purposes — of the duct system in a patient after removal of the gall bladder. Since the introduction of Telepaque the duct system has been more commonly seen, but the experience of most investigators is that Cholografin is far more efficient than Telepaque. The contrast medium is poorly concentrated in patients with severe liver damage and in most patients with jaundice. For this reason most authors advise against the use of the drug in such cases. Occasionally, filling of the bile ducts is not seen in patients who have no demonstrable liver damage or other known reason.

A few cases of severe chills have been reported in the German literature. No severe reactions have been described in this country, to date. Caution, however, should be used as with any of the intravenously administered drugs with high iodine content. Some reactions may occur in the future.

It is safe to predict that this examination will be done with increasing frequency in cases in which the oral Graham test is inconclusive or shows nonfilling of the gall bladder. Even with this new drug density of the bile ducts is often not sufficient for detail studies. Other mediums that are still more markedly concentrated by the liver are to be hoped for.

The re-formed gall bladder. If the cystic duct is not ligated close to its junction with the common duct, it may become progressively enlarged after cholecystectomy, to the extent that it is in effect a small re-formed gall bladder.[127] This phenomenon may account for postcholecystectomy symptoms, and the stones may either be left in the cystic-duct stump or form there after removal of the gall bladder. These stones may be visible on plain films of the abdomen, and have been seen as filling defects in a dye-filled stump when a Graham test is done.[128,129]

This distressing complication can be avoided by ligation of the cystic duct at its junction with the common duct,[130] and the junction can be most accurately located by cholangiography at the time of operation.

Liver

Search for a substance that is nontoxic and not radioactive and will opacify the liver has so far been unsuccessful. Thorotrast has been abandoned, not only because of its danger as a carcinogenic substance, but also because its radioactivity produces extensive hepatic fibrosis.[131] Olsson and Ekman[132] have used various halogenated fatty acids experimentally, and although some opacify the liver, they are too toxic for clinical use.

Various methods of portal venography have been proposed, and, of these, rapid percutaneous injection of Diodrast or a similar contrast substance into the spleen seems the most innocuous.[133] Direct injection into the portal system is, of course, done with ease when the abdomen is open.[134,135] At present portal venography is most frequently done preliminary to portacaval shunt, and the result may dictate whether the anastomosis is made between the splenic and renal veins or between the portal vein and the vena cava.

Pancreas

A number of groups continue to search for a good method to visualize the pancreas. Until such a method is found, diseases of this organ will remain difficult to detect. Calcification in the pancreas is sometimes seen in chronic pancreatitis, and its major ducts can sometimes be demonstrated as a part of the cholangiography. Otherwise, disease cannot be detected radiologically until it manifests itself by affecting surrounding organs such as the duodenum and stomach.

References

Duodenum

51. Templeton, F. E. Crater in uncomplicated duodenal ulcer. *Am. J. Roentgenol.* **59**:87-89, 1948.
52. Ettinger, A. Duodenal ulcers simulating prepyloric lesions. *Am. J. Roentgenol.* **64**:603-609, 1950.
53. Ball, R. P., Segal, A. L., and Golden, R. Post bulbar ulcer of duodenum. *Am. J. Roentgenol.* **59**:90-99, 1948.
54. Erb, W. H., and Johnson, T. A. Hyperplasia of Brunner's glands simulating duodenal polyposis. *Gastroenterology* **11**:740-745, 1948.
55. Dodd, G. D., Fishler, J. S., and Park, O. K. Hyperplasia of Brunner's glands. *Radiology* **60**:814-821, 1953.
56. Hannan, J. R., Hazard, J. B., and Wise, R. E. Carcinoid of duodenum. *Am. J. Roentgenol.* **66**:569-576, 1951.

Small Intestine

57. Friedman, J., and Rigler, L. G. Method of double contrast roentgen examination of small intestine. *Radiology* **54**: 365-379, 1950.
58. Dedick, A. P., and Collins, L. C. Roentgen diagnosis of bleeding lesions of small intestine. *Am. J. Roentgenol.* **69**:926-935, 1953.
59. Teitelbaum, M. D., and Arenson, N. Recurrent small intestinal intussusception in children. *Am. J. Roentgenol.* **63**:80-88, 1950.
60. Hellmer, H. Intussusception in children: diagnosis and therapy with barium enema. *Acta radiol.* Supp. **85**:1-120, 1948.
61. Ravitch, M. M., and McCune, R. M., Jr. Intussusception in infants and children. *J. Pediat.* **37**:153-173, 1950.
62. Girdany, B. R., Bass, L. W., and Grier, G. W. Reduction of ileocecal intussusception by hydrostatic pressure. *Radiology* **60**: 518-526, 1953.
63. Whitmore, W. H., and Peterson, G. M. Henoch's purpura: small intestinal changes: case report. *Radiology* **46**:373-376, 1946.
64. Esposito, J. J. Small intestinal abnormalities in anaphylactoid purpura. *Radiology* **55**:548-551, 1950.
65. Fetter, J. S., and Mills, W. L. Roentgenographic findings in Schönlein-Henoch's purpura. *Radiology* **55**:545-547, 1950.
66. Jacobson, G., and Carter, R. A. Small intestinal rupture due to non-penetrating abdominal injury: roentgenological study. *Am. J. Roentgenol.* **66**:52-64, 1951.
67. Koenig, E. C., and Culver, G. J. Retroperitoneal perforation of duodenum: report of case. *Radiology* **48**:164-167, 1947.
68. Primann-Dahl, J. C. *Roentgen Examinations in Acute Abdominal Diseases.* 321 pp. Springfield, Illinois: Thomas, 1951.
69. *Idem.* Roentgen examination in mesenteric thrombosis. *Am. J. Roentgenol.* **64**:610-616, 1950.
70. Lockwood, I. H., Smith, A. B., and Walker, J. W. Acute small intestinal obstruction. *Radiology* **51**:310-318, 1948.
71. Cantor, M. O. Radiological criteria for removal of intestinal decompression tube. *Radiology* **54**:535-540, 1950.
72. Janus, W. L. Regional jejunitis. *Radiology* **50**:532-535, 1948.
73. Marshak, R. H., and Wolf, B. S. Chronic ulcerative granulomatous jejunitis and ileojejunitis. *Am. J. Roentgenol.* **70**:93-113, 1953.
74. Anderson, C. M., Astley, R., French, J. M., and Gerrard, J. W. Small intestine pattern in coeliac disease. *Brit. J. Radiol.* **25**: 526-530, 1952.
75. Frazer, A. C., French, J. M., and Thompson, M. D. Radiographic studies showing induction of segmentation pattern in small intestine in normal human subjects. *Brit. J. Radiol.* **22**: 123-136, 1949.
76. Goin, L. S. Some obscure factors in production of unusual small bowel patterns. *Radiology* **59**:177-184, 1952.
77. Lerner, H. H., Levinson, S. S., and Kateman, A. E. Meckel's diverticulum, new roentgen diagnostic sign and case report. *Am. J. Roentgenol.* **69**:268-271, 1953.

Colon

78. Hamilton, J. B. Use of tannic acid in barium enemas. *Am. J. Roentgenol.* **56**:101-103, 1946.
79. Christie, A. C., Coe, F. O., Hampton, A. O., and Wyatt, G. M. Value of tannic acid enema and post-evacuation roentgenograms in examination of colon. *Am. J. Roentgenol.* **63**:657-664, 1950.
80. Stevenson, C. A. Development of colon examination. *Am. J. Roentgenol.* **71**:385-397, 1954.
81. Stevenson, C. A., and McClure, W. Indications for double contrast colon examination. *Am. J. Roentgenol.* **71**:398-403, 1954.
82. Templeton, F. E., and Addington, E. A. Roentgenologic examination of colon using drainage and negative pressure, with special reference to early diagnosis of neoplasm. *J.A.M.A.* **145**:702-704, 1951.
83. Gianturco, C., and Miller, G. A. Routine search for colonic polyps by high-voltage radiography. *Radiology* **60**:496-499, 1953.
84. Potter, R. M. Dilute contrast media in diagnosis of lesions of colon. *Radiology* **60**:500-509, 1953.
85. Moreton, R. D. Double-contrast examination of colon with special emphasis on studies of sigmoid. *Radiology* **60**:510-517, 1953.
86. Ettinger, A., and Elkin, M. Study of sigmoid by special roentgenographic views. *Am. J. Roentgenol.* **72**:199-208, 1954.
87. Sharpe, M., and Golden, R. End-to-end anastomosis of colon following resection. *Am. J. Roentgenol.* **64**:769-777, 1950.
88. Euphrat, E. J. Roentgen features of mucocele of appendix. *Radiology* **48**:113-117, 1947.
89. Childe, A. E. Calcified appendiceal fecal concretions in childhood. *Am. J. Roentgenol.* **58**:455-463, 1947.
90. Thomas, S. F. Appendiceal coproliths: their surgical importance. *Radiology* **49**:39-49, 1947.

91. Felson, B., and Bernhard, C. M. Roentgenologic diagnosis of appendiceal calculi. *Radiology* **49**:178-191, 1947.
92. Young, E. L., Morrison, H. R., and Wilson, W. E., Jr. Volvulus of cecum and ascending colon. *New Eng. J. Med.* **237**:78-86, 1947.
93. Donhauser, J. L., and Atwell, S. Volvulus of cecum. *Arch. Surg.* **58**:129-148, 1949.
94. Bellini, M. A. Volvulus of sigmoid: new radiologic sign. *Radiology* **53**:268-270, 1949.
95. Bruusgaard, C. Volvulus of sigmoid colon and its treatment. *Surgery* **22**:466-478, 1947.
96. Isaacson, N. H., and Greer, D. B. Conservative treatment of acute form of sigmoid volvulus. *Surgery* **31**:544-551, 1952.
97. Kalil, T. H., and Robbins, L. L. Early roentgenologic changes in idiopathic ulcerative colitis. *Radiology* **53**:1-10, 1949.
98. Kirsner, J. B., Palmer, W. L., and Klotz, A. P. Reversibility in ulcerative colitis: clinical and roentgenologic observations. *Radiology* **57**:1-14, 1951.
99. Shands, W. C., Dockerty, M. B., and Bargen, J. A. Adenocarcinoma of large intestine associated with chronic ulcerative colitis: clinical and pathologic features of 93 cases. *Surg., Gynec. & Obst.* **94**:302-310, 1952.
100. Swenson, O. Modern treatment of Hirschsprung's disease. *J.A.M.A.* **154**:651-653, 1954.
101. Swenson, O., Neuhauser, E. B. D., and Pickett, R. K. New concepts of etiology, diagnosis and treatment of congenital megacolon (Hirschsprung's disease). *Pediatrics* **4**:201-209, 1949.
102. Jolleys, A. Death following barium enema in child with Hirschsprung's disease. *Brit. M. J.* **1**:692, 1952.
103. Hollingsworth, C. Haemangiomatous lesions of colon. *Brit. J. Radiol.* **24**:220-222, 1951.

Liver and Biliary System

104. Waggoner, C. M., and LeMone, D. V. Clinical and roentgen aspects of internal biliary fistulas: report of 12 cases. *Radiology* **53**:31-41, 1949.
105. Culver, G. J., and Kline, J. R. Acute gaseous cholecystitis: report of case. *Radiology* **50**:536-538, 1948.
106. Heifetz, C. J., and Senturia, H. R. Acute pneumocholecystitis. *Surg., Gynec. & Obst.* **86**:424-433, 1948.
107. Friedman, J., Aurelius, J. R., and Rigler, L. G. Emphysematous cholecystitis. *Am. J. Roentgenol.* **62**:814-822, 1949.
108. Hinkel, C. L. Fissures in biliary calculi: further observations. *Am. J. Roentgenol.* **71**:979-987, 1954.
109. Sosman, M. C. Radiologic aspects of gall-bladder disease. *New Eng. J. Med.* **231**:786-794, 1944.
110. Morales, O., and Swedberg, J. Cholecystography and surgical findings. *Acta radiol.* **31**:44-50, 1949.
111. Greenwood, F., and Samuel, E. Pathological gall bladder. *Brit. J. Radiol.* **21**:438-445, 1948.
112. Christensen, W. K., and Sosman, M. C. Preliminary report on telepaque, new cholecystographic medium. *Am. J. Roentgenol.* **66**:764-768, 1951.
113. Kirklin, B. R. New position for cholecystography. *Am. J. Roentgenol.* **60**:263-268, 1948.
114. Latimer, E. O., Mendez, F. L., Jr., and Hage, W. J. Congenital absence of gallbladder. *Ann. Surg.* **126**:229-242, 1947.
115. Braun, A., and Wischnewsky, A. W. Cited by Golob, M., and Kantor, J. G. Two cases of double gall bladder. *Am. J. Digest. Dis.* **9**:120-123, 1942.
116. Silvani, H. L., and McCorkel, H. J. Temporary failure of gallbladder visualization by cholecystography in acute pancreatitis. *Ann. Surg.* **127**:1207-1211, 1948.
117. Mixter, C. G., Hermanson, L., and Segel, A. L. Operative cholangiography. *Ann. Surg.* **134**:346-350, 1950.
118. Hight, D., and Lingley, J. R. Value of cholangiograms during biliary-tract surgery. *New Eng. J. Med.* **246**:761-765, 1952.
119. Hicken, N. F., McAllister, A. J., Franz, B., and Crowder, E. Technic, indications and value of postoperative cholangiography. *Arch. Surg.* **60**:1102-1113, 1950.
120. Rigler, L. G., and Mixer, H. W. Cholangiography and biliary regurgitation. *Radiology* **48**:463-471, 1947.
121. Twiss, J. R., Beranbaum, S. A., Gillette, L., and Poppel, M. H. Post-cholecystectomy oral cholangiography: preliminary report. *Am. J. M. Sc.* **227**:372-386, 1954.
122. Shehadi, W. H. Oral cholangiography with Telepaque. *Am. J. Roentgenol.* **72**:436-451, 1954.
123. Frommhold, W. Ein neuartiges Kontrastmittel für die intravenöse Cholezystographie. *Fortschr. a.d.Geb.d.Röntgenstrahlen* **79**:283-291, 1953.
124. Berk, J. E., Karnofsky, R. E., Shay, H., and Stauffer, H. M. Intravenous cholecystography and cholangiography: report of preliminary observations. *Am. J. M. Sc.* **227**:361-371, 1954.
125. Bell, A. L. L., Immerman, L. L., Arcomano, J. P., Zwanger, J., and Bello, E. T. Intravenous cholangiography. *Am. J. Surg.* **88**:248-253, 1954.
126. Orloff, T. L., Sklaroff, D. M., Cohn, E. M., and Gershon-Cohen, J. Intravenous cholecholecystography with new contrast medium, "Cholografin." *Radiology* **62**:868-870, 1954.
127. Hicken, N. F., White, L. B., and Coray, Q. B. Incomplete removal of cystic duct as factor in producing postcholecystectomy complications. *Surgery* **21**:309-320, 1947.
128. Weingarten, M. Calculi in dilated stump of cystic duct, preoperative visualization. *J.A.M.A.* **145**:157-159, 1951.
129. Bauer, W. B. A. J. Postcholecystectomy complications due to incomplete removal of gallbladder and cystic duct. *Arch. Surg.* **63**:612-616, 1951.
130. Livingston, H. J., and Livingston, S. F. "Re-formed gallbladder" with stones following cholecystectomy 17 years ago. *Arch. Int. Med.* **89**:961-966, 1952.
131. Thomas, S. F., Henry, G. W., and Kaplan, H. S. Hepatolienography: past, present and future. *Radiology* **57**:669-683, 1951.
132. Olsson, O., and Ekman, B. Oral hepatography: preliminary report of experimental study. *Acta radiol.* **31**:33-36, 1949.
133. Walker, R. M., Middlemiss, J. H., and Nanson, E. M. Portal venography by intrasplenic injection. *Brit. J. Surg.* **40**:392-395, 1953.
134. Moore, G. E., and Bridenbaugh, R. B. Roentgen demonstration of venous circulation in liver: portal venography. *Radiology* **57**:685-690, 1951.
135. Child, G. G., O'Sullivan, W. D., Payne, M. A., and McClure, R. D., Jr. Portal venography. *Radiology* **57**:691-701, 1951.

MEDICAL INTELLIGENCE

HERNIATION OF FAT THROUGH LUMBODORSAL FASCIA AS A CAUSE OF LOW-BACK PAIN*

CHARLES D. BONNER, M.D.,† AND S. CHARLES KASDON, M.D.‡

BOSTON

THE syndrome discussed in this paper is not new. The following case is reported, however, because it illustrates some of the diagnostic difficulties encountered when there is a history of unexplained, severe and incapacitating pain.

*From the Cancer Research and Cancer Control Unit, Department of Surgery, the Department of Medicine and the Department of Gynecology, Tufts College Medical School.

†Instructor in medicine, Tufts College Medical School; instructor in medicine, Boston University School of Medicine; trainee, National Cancer Institute, National Institutes of Health.

‡Associate clinical professor of gynecology and clinical investigator, Cancer Research and Cancer Control Unit, Tufts College Medical School; chief-of-staff, Booth Memorial Hospital, Brookline, Massachusetts.

Case History

A 67-year-old obese woman was 1st admitted to a hospital in July, 1952, with the chief complaint of "pain in the region of the left buttock radiating medially to the tip of the spine." The pain had been present for 4 months, restricting her daily activities. At night she slept well, without pain. No orthopedic lesion could be found to account for the complaints. During the hospital stay it was noted that she had a cancer phobia and was extremely apprehensive about the possibility of a malignant neoplasm some place in her body. After full evaluation and an explanation that no neoplasm could be found, her spirits rose, and her symptoms decreased. She was discharged on the 5th hospital day, to be followed in the outpatient-department orthopedic clinic. The discharge diagnosis was osteoarthritis.

She was next seen in September in the medical clinic of another hospital because of the same complaint. An x-ray examination of the lower spine revealed "minimal to moderate osteoarthritic changes about the margins of the vertebral bodies." Heat, aspirin, a flat mattress and phenobarbital were recommended. At the fracture clinic in October she was referred to the Department of Physical Medicine, where she received physiotherapy twice; heat, aspirin, a flat mattress and a corset were then recommended. She was seen again in the medical clinic in November with the same complaints, and the "basic features of therapy were again reviewed for her, and she was advised to return if necessary." The diagnosis, again, was osteoarthritis.

She was admitted to still another hospital in January,

1953, from its own outpatient department, where she had complained of intractable pain in the left flank or left hip so persistently that she was admitted on the advice of the hiatus hernia, and x-ray examination of the lumbar spine showed rotary scoliosis to the left. Reactive changes were noted about the articular facets between the 4th and 5th

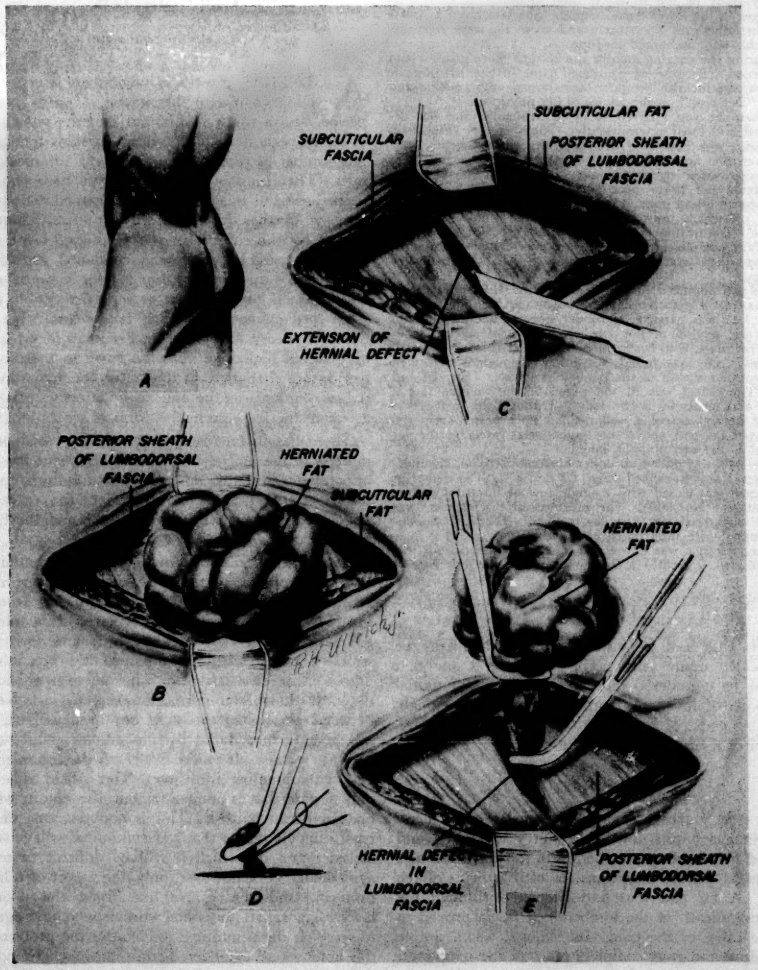


FIGURE 1. *Mechanism and Correction of Herniation, Showing the Incision in the Left Lumbar Area above the Buttock* (A), *with the Transverse Incision in the Subcuticular Fascia and the Lobulated Mass of Moderately Well Defined Fat* (B), *the Extension of the Defect in the Posterior Sheath of the Fascia (the Lobulated Mass Is Not Shown in this Drawing)* (C), *and the Pedicle Transected above a Clamp* (D) *and Pulled up with Moderate Force* (E).

neurology clinic for study. Procedures in the outpatient department had included a sigmoidoscopy, a barium-enema examination and an intravenous pyelogram. In the hospital an upper gastrointestinal x-ray series revealed a small lumbar vertebras, especially on the left side. The intervertebral spaces demonstrated nothing unusual. In the lower dorsal area there was evidence of osteoarthritis. Pedicles, so far as they could be seen, disclosed nothing un-

usual. The patient was discharged after 17 days with the diagnosis of osteoarthritis of the spine.

In April she was admitted to a 4th hospital complaining of pain in the lower back, urinary frequency and urgency. X-ray study of the spine revealed moderate osteoarthritic changes in the lower dorsal region. She was given a course of physiotherapy; a cystocele and rectocele were repaired, and she was discharged in June.

During the ensuing months she became more inactive and depressed. Because of continued pain in the left lumbar region, she took an "empirin" compound with codeine and then "Demerol," on the advice of her physicians.

When she was referred to us in September she was depressed and cried intermittently. She was very definite in localizing her pain and describing its characteristics. She touched her finger to one place and stated that the pain was aggravated by movement. During the physical examination her lower back was palpated. In the precise spot that she had pointed out there was a deep, firm, tender mass, on which pressure reproduced the whole pain syndrome. Infiltration of this area with 10 cc. of 1 per cent novocain completely abolished the pain for several hours. She was then referred to one of us (S.C.K.) for definitive therapy.

She was admitted to the New England Hospital on September 14. Operative exploration of the left lumbar area (Fig. 1*A*) was carried out under general anesthesia. On transverse section of the subcuticular fascial layer a lobulated fat mass, 6 to 8 cm. in diameter and moderately well circumscribed, was found protruding through a defect in the posterior sheath of the lumbodorsal fascia (Fig. 1*B* and *C*). The defect was in the plane of the oblique fascial fibers and measured 3 cm. long. Through the midportion of the hernial defect a well defined stalk passed from the lobulated fat pad above the lumbodorsal fascia to the fat overlying the sacrospinalis muscle.

The stalk was pulled up under moderate tension, clamped, transected and transfixed (Fig. 1*D* and *E*). The defect in the fascia was closed with a single row of interrupted fine-silk sutures (No. 000). The subcuticular fascial layer was closed transversely in a similar manner. The skin was approximated with interrupted black-silk sutures.

Convalescence was uneventful and when the patient was re-examined 6 months after the operation she was free of pain.

Discussion

This case and its history could undoubtedly be duplicated many times. The syndrome is one that should be considered more often in the differential diagnosis of low-back pain. Encouragingly enough, it is one cause of back pain for which the physician can offer a simple and definite cure.

Summary

An elderly obese female who complained of incessant incapacitating low-back pain was studied and treated for over fourteen months in four hospitals and by several private physicians for osteoarthritis of the spine. A fat pad that had herniated through the posterior sheath of the lumbodorsal fascia proved to be the cause of the pain. Its removal was a simple procedure and gave complete relief of the symptoms. The case points out the importance of including the syndrome among the possible causes of low-back pain.

BY THE LONDON POST

Morals and the Law — The Doctor's Office

John Lister, M.D.

London, England

A GENERAL growth of lawlessness is one of the well recognized phenomena of any postwar period, and a study of criminal statistics reveals that in recent years there has been an alarming increase in the number of prosecutions for serious offenses of all sorts. The rising prevalence of male homosexuality is one aspect of this trend that has caused widespread concern. Earlier this year Lord Winterton initiated a debate on the subject in the House of Lords. He vigorously attacked any who condoned the homosexual crime and bitterly opposed the views of those who contend that, because of some irresistible urge, some men cannot help being homosexual. He said that this theory was based on Freudian ideas, which he believed had done immense harm to the modern world. He thought that a greater condemnation by public opinion was the only really effective means of arresting the increase in this form of vice.

There has in fact been a greatly increased public interest in the matter, and the Government has now appointed an official committee to inquire into the prevalence of homosexual behavior, the extent to which it results in punishable offense and the treatment of offenders.

Commenting on the problem facing the committee, the *Times* points out that the crucial problem is not whether homosexual relations are sinful but whether the law should punish them as such. It would be generally agreed that the law must interfere with sexual behavior when there is assault, when advantage is taken of children, or when there is public indecency. In this country, however, when relations between persons of the same sex are involved, the law goes further if the persons are men, but not if they are women. It punishes severely private relations between consenting adult men. This is held to be not only a state that is anomalous but also one in which blackmail can flourish. This is doubtless one of the most difficult points that the committee will have to consider and on which it will be difficult to reach agreement. It is, however, only one aspect of a large problem, and the *Times* has urged the doctors, lawyers, moralists and social workers who have agreed to serve on the committee to consider the problem of the homosexual offender against the background of the varieties of sexual behavior prevalent among ordinary noncriminal citizens.

Another topic much discussed at present is the question of the strip cartoons portraying scenes of horror that have become such an ugly feature of bookstalls on both sides of the Atlantic. The "penny dreadful" of the Victorian era has certainly undergone a frightful process of degeneration, and in recent weeks there have been many articles and letters in the national press on the evil effects that the worst of these so-called comics are having on adolescents and children. A glorification of crime, a morbid preoccupation with death, killings by werewolves and ghouls and a frank exploitation of the sexual instinct are some of the more vicious themes. Indeed, these "comics" have been described as primers in crime and the *Daily Telegraph* in a leading article entitled "Child Guidance in Brutality," has condemned the diet of horror that some of them provide. The *British Medical Journal* has said that no family doctor can remain indifferent to attempts to present to the minds of readers scenes of horror, terror and violence.

The education authorities have become so disturbed by the problem that the National Union of Schoolteachers has staged an exhibition of comics read by schoolchildren all over the country. The exhibition has been visited by church leaders and Government officials, who have been able to see a large variety of exhibits ranging from harmless comics with titles like "Mickey Mouse" and "Tiny Tots" to lurid pictures showing the worst kind of horror.

The Home Secretary has received a deputation led by the Archbishop of Canterbury asking him to take action, and he has been asked in Parliament to ban horror comics on grounds of obscenity. The difficulty on this point seems to turn on the definition of obscenity. There is an impression abroad that it refers only to sexual immorality, but Sir Alan P. Herbert, in a letter to the *Times,* has tried to dispose of this fallacy. He recalls a case in 1868 in which Chief Justice Cockburn said that the test of obscenity is whether "the tendency of the matter charged is to deprave and corrupt those whose minds are open to such immoral influences and into whose hands a publication of this sort may fall."

On this definition it certainly seems that the horror comic should be brought within the law.

* * *

Recent surveys, such as that carried out by Dr. Hadfield for the British Medical Association, have shown that the standard of doctors' office accommodation varies greatly up and down the country. The consulting rooms of the consultants and specialists in Harley Street are sumptuously appointed, and private consultation fees are proportionately high. The National Health Service doctor, who has to see large numbers of State patients who have a varying degree of respect for his property, must naturally provide accommodation of a different type. Many practices have now very adequate premises, especially when several doctors are working together in a group practice. It is unfortunately true that a minority of doctors do not provide the standard of accommodation that their contract in the Health Service requires. It is for this reason that the Minister of Health has ordered an inspection of the waiting rooms and offices of all general practitioners in the National Health Service. The Ministry has agreed that the inspection shall be carried out by the doctors themselves under the guidance of the local executive councils of the National Health Service. The standards to be adopted will vary with the type of practice and with local traditions, and it is hoped that the members of the inspecting teams will exercise restraint and tact and that they will spend time and trouble in carrying out the survey.

It is certainly important if there are bad conditions to know how bad and how widespread they are. It is also a concession that the Ministry has agreed to allow the doctors to carry out this survey, and it cannot be denied that in a public service there must be powers that can demand inspections such as this. Nevertheless, it makes one tremble to think of the effects on the medical profession if such powers should ever be abused.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40521

PRESENTATION OF CASE

A forty-six-year-old widow entered the hospital because of pain over the right scapula.

About five months before admission she noticed the gradual onset of a steady, continuous, knifelike pain along the upper vertebral border of the right scapula that increased in severity, was aggravated by motion of the right arm and was relieved by rest, aspirin and local application of heat. Three weeks after the onset, she was examined in the clinic. Marked tenderness was elicited over the upper inner part of the right scapula, which had some limitation of motion. There was no local heat or swelling. The lungs showed slight dullness and occasional rales at the right apex. Roentgenograms of the chest revealed an area of increased density with a suggestion of cavity formation in the right apex (Fig. 1). This was not present in a film taken four years previously, when calcified nodules were seen in the left apex and both hili. The finding of a cavity, 3 by 5 cm., with a thick wall was confirmed by a laminogram taken three weeks later (Fig. 2). At about the same time, a bronchoscopy was performed, but no lesion was found. The bronchial washing was negative for tubercle bacilli on smear and by culture and guinea-pig inoculation. Cytologic examination for tumor cells was also negative. Three subsequent gastric washings and one sputum were all negative for tubercle bacilli; however, a tuberculin test (1:10,000 dilution) gave a strongly positive reaction. The pain over the scapula increased in severity and required codeine for relief. During the week before admission there was also pain on coughing. The patient denied dyspnea, hemoptysis, production of sputum, night sweats or increased fatigability. She had lost about 8 pounds in weight. Slight ankle edema had been noticed since the onset of the pain in the scapula. A coccidioidin test was negative.

The patient was born in Ireland and came to the United States thirty years before admission. The past history was noncontributory except for an attack of "pneumonia" eleven years before admission. Her husband had died five years previously of pulmonary tuberculosis. Five children were living and well.

Physical examination revealed a thin and somewhat pale woman in no apparent distress. Over the right side of the back medial to the scapular spine there was an area of hyperesthesia and deep tenderness; when it was struck severe pain extended from it laterally and down through the entire right arm to the wrist. There were diminished resonance, slight bronchovesicular breathing and occasional inspiratory and expiratory rales at the apex of the right lung posteriorly. The heart and the abdomen were normal. There was slight tenderness at the right axilla and the medial aspect of the right upper arm. The motor function of the arms was equal and strong. The ankles were slightly edematous.

The temperature was 97.6°F., the pulse 88, and the respirations 22. The blood pressure was 126 systolic, 74 diastolic.

Urinalysis was negative. The hemoglobin was 12.5 gm. per 100 cc., and the white-cell count 7500. A roentgenogram of the chest again disclosed a large cavity in the apical segment of the right upper lobe that had changed only slightly since the examination four months previously. The wall appeared thicker, but there was no change in the size of the cavity. Roentgenograms of the right shoulder, cervical and dorsal spines and right elbow showed no destructive lesion.

On the seventh hospital day, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. THEODORE L. BADGER*: Obviously, the diagnosis had not been made up to the time that the operation was performed. I think that the outstanding feature of the lesion was its presence with a great deal of pain and very few other symptoms or signs except for some dullness and a few rales. I am always bothered by trying to determine how pain gets into the arms, wrists, hands and lungs. I am not sure in this case how it did. The tenderness, if I understand it correctly, was above the level of the scapular spine and medial to it; therefore, I should think it was in the region of the second, third and fourth thoracic nerves, and I suppose that by that route it got to the brachial plexus. I do not know whether it went down beyond the antecubital nerves to the wrist. I reviewed the distribution of the nerves last night, but when I got through I was not at all sure that I understood the reflex action any better than I did before I started. I believe that the antecubital nerve stops at the wrist.

*Chief of Medical Thoracic Clinic, Boston City Hospital; clinical associate in medicine, Massachusetts General Hospital.

The source of the pain is also not clear. I think the source of pulmonary pain is not always clear anyway. Actually, the endings of the sympathetic and vagal nerves of the lungs are quite plentiful. Miller[1] has shown that those nerves, which travel along the posterior portion of the lung and along the bronchi and pulmonary veins, supply nerve endings all the way down the bronchial mucosa to the atria and in the musculature to the alveolar ducts. Ordinarily, one does not expect much sensation of pain from these areas, but any hollow organ that is distorted, compressed or distended anywhere in the body gives pain. I am not sure it is as easy to analyze the origin and distribution of the pain as it is to conceive of it. I do not know why this patient had so much pain. There appears to have been no bony destruction associated with the pulmonary lesion if the x-ray findings are correct. I leave this for our roentgenologists to confirm or disprove, but there is often pain from the bones where no destructive lesions are visible for some time after the metastatic or destructive process has occurred.

Are we dealing with tuberculosis, coccidioidomycosis, histoplasmosis, a cyst of the lung, lung abscess or carcinoma? I am inclined to believe that we are not dealing with tuberculosis. Nothing was said about the nature of the therapy. I should deduce that, if the patient had received specific antituberculosis chemotherapy, the lesion would have improved considerably in a period of four months; if she received no specific therapy, it should have grown worse under those conditions. Because no comment was made about her being restricted in activity, I should expect that no tubercle bacilli were found.

FIGURE 1. *Cavity in Right Upper Lobe (Arrow), Shown in Apical Projection.*

DR. HELEN S. PITTMAN: I do not see any evidence in the record that she was receiving antituberculosis therapy. The discharge note when she came in for bronchoscopy included the recommendation that she rest for four to six hours during the day.

DR. BADGER: No specific therapy was applied.

DR. PITTMAN: She was given codeine and aspirin.

DR. BADGER: I shall let my deductions about the change in size and the progression of the process stand. I take it that there was a single ringlike cavity without much else in the lung itself. I am inclined to think that it was not tuberculosis because of the good efforts that were made to find tubercle bacilli. Moreover, the pain was unduly severe. I do not think that pain associated with tuberculosis is as severe as the pain of which this woman complained. It was not particularly pleuritic but was described as knifelike. I am not sure what the distinction between knifelike and pleuritic is. I have always regarded pleuritic pain as knifelike myself, but there may be another term that would describe it better. If the tuberculin test had been negative, it would be more useful. The positive tuberculin test merely indicates the presence of tubercle infection at one time or other and is a demonstration of skin allergy to the presence of tubercle bacilli. It does not tell us anything whatsoever about the anatomic extent or the activity or

FIGURE 2. *Laminogram of the Right Upper Lobe of the Lung, Showing the Diffuse Density in the Extreme Apex and the Thick-Walled Cavity.*
Arrows indicate the lateral margin of the cavity.

inactivity of the disease. Therefore, the positive tuberculin test indicates that the patient in her forty-six years had at some time been exposed to tuberculosis and is consistent with the fact that she was known to have had calcification at an earlier date.

About coccidioidomycosis, I think the size of the cavity was unlike that in coccidioidomycosis. Although the coccidioidin skin test was negative, I should consider that to be inadequate and would have wanted to know what the sputum planted on Sabouraud's medium showed. Positive cultures for *Coccidioides immitis* are frequent in the presence of a negative skin test. I take it that the patient had lived here and had not been out of this part of the country. Is that correct?

DR. PITTMAN: Yes.

DR. BADGER: I should say that histoplasmosis was unlikely, but it can do anything; it can reproduce tuberculosis or coccidioidomycosis. At the time a histoplasmosis test may or may not have been done. Such tests when negative are probably important; if not a complement-fixation test should be done to indicate more specifically whether or not the infection is active if present. I gather that that was not done and was not considered.

Another thing that I certainly should consider

before I see the x-ray films is cystic disease of the lung, especially that which had developed on an acute infection and was closely similar to a lung abscess. I should say that the symptoms more or less disproved that idea since there was little or no sputum. Although the amount is not recorded, I take it that it was not much. Is that correct?

DR. PITTMAN: There was only a very small amount.

DR. BADGER: It is unlikely that I am dealing with a lung abscess. May I see the x-ray films?

DR. JOSEPH HANELIN: In the films taken four years previously the right apex is entirely clear. I think the description of a possible lesion at the left apex may have been an error; I suspect it is an artifact, for I cannot see it in the later films.

There are a number of calcified densities at the root of the right lung. Four years later the lesion described in the protocol is well visualized in the apical views (Fig. 1) and particularly in the laminograms (Fig. 2). There is a relatively thick-walled ovoid cavity, 5 cm. in greatest dimension, that is continuous with a diffuse density at the extreme right apex. In the lateral projection the cavity can be visualized lying posteriorly. An anteroposterior view of the lower cervical and upper thoracic regions suggests minimal lytic destruction of the right transverse process of the second thoracic vertebra; otherwise, I cannot make out any bony involvement. The films of the chest four months later show findings essentially the same, with only questionable further extension of the apical density superior to the cavity.

DR. BADGER: If I were presented with those x-ray films and no history of the patient and were asked to make a diagnosis I should say, "I do not know." It looks entirely consistent with tuberculosis, a lung abscess, carcinoma or underlying cystic disease, all of which are difficult to distinguish from each other by x-ray examination alone. I consider the primary diagnosis to be carcinoma of the lung, because the course was relatively asymptomatic except for the long-continued pain. It has been my experience that when a pain has been present as long as this and has been as constant as this and a diagnosis of tuberculosis has been made, it has almost always been wrong. Under these circumstances, in a woman of forty-six years, the diagnosis most logically made is cancer of the lung. I do not know how anyone can decide that tuberculosis may not have been present at the same time. It is quite likely that both existed. Recently, at the Veterans Administration Hospital, we had a patient with a cavity in the left apex in the infraclavicular area, who had less pain and less induration than this woman had. We thought for a short time that it was tuberculosis. We only waited for two weeks, however, before operation revealed carcinoma of the lung. In the case under discussion here, if tubercle bacilli had been demonstrated at any time before surgery, it would still be logical to consider the primary diagnosis carcinoma because of the severity of the pain. Operation was indicated without any question. The absence of carcinoma cells in the bronchial smear means practically nothing with the symptoms and x-ray picture presented. Operation was wisely performed to establish the diagnosis.

DR. BENJAMIN CASTLEMAN: Dr. Pittman, have you any comment?

DR. PITTMAN: This woman had been seen in the clinic four years before admission; a year previously her husband had died of tuberculosis. A lesion was found on the left, and according to the record the diagnosis of inactive tuberculosis of the left lung was made. She was not seen again until she presented herself with pain and was studied in the clinic. When she was seen at Pulmonary Rounds the consensus was that the lesion in the right apex represented either tuberculosis or tumor and that surgical exploration should not be delayed.

DR. WILLIAM H. BAKER: Was she a heavy smoker?

DR. PITTMAN: I do not find any note about that. The diagnoses of abscess and coccidioidomycosis were considered; histoplasmosis was not considered.

CLINICAL DIAGNOSIS

?Tuberculous cavitation, apex of right lung.

DR. THEODORE L. BADGER'S DIAGNOSIS

Carcinoma of lung.

ANATOMICAL DIAGNOSIS

Adenoacanthoma, apex of right lung, with cavitation and involvement of parietal pleura.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. J. Gordon Scannell, who operated on this patient, found, as one might have expected, a great deal of adherence between the apex of the lung and the posterolateral wall of the chest, which he had a difficult time in dissecting. At the time of the operation Dr. Scannell gave us a piece of the thickened pleura for a rush frozen section; it proved to be adenocarcinoma. He finally resected the right upper and middle lobes. The specimen revealed the large cavity covered with the markedly thickened pleura. Its walls were thick, fibrotic and very shaggy and irregular on the inside, with raised, corrugated foci. Our sections show only a carcinoma without any evidence of tuberculosis. We looked quite carefully for that because on occasion we have found the two in combination. There was keratinization of part of the tumor so that, morphologically, it was an adenoacanthoma rather than a straight adenocarcinoma. Microscopical sections of the pleura disclosed a cause of the pain — extensive perineural infiltration by the carcinoma (Fig. 3).

The tumor had invaded not only the nerves but also the blood vessels. In one vessel there was a tumor thrombus that was organized and recanalized. All these findings indicate a poor prognosis. I do not believe the cancers in the apexes of the lung with a Pancoast syndrome have ever been cured. Although this patient did not have a true Horner syndrome, the fact that she had pain going down to the scapular region indicates that the tumor had gone outside the lung. In a review of all the reported cases of Pancoast or superior-sulcus tumors by Herbut and Watson[2] no survivals were found. Under those circumstances I should wonder about the value of an operation. In this particular case if tuberculosis was also found would you attempt to remove a cavity of that size, Dr. Badger?

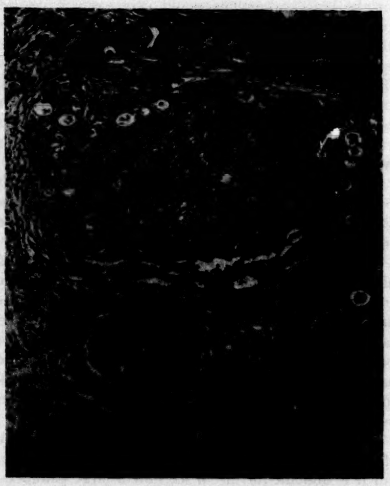


FIGURE 3.

DR. BADGER: Not without adequate treatment for several months.

DR. CASTLEMAN: The patient is receiving x-ray treatment and seems to be fairly comfortable.

DR. BADGER: The original Pancoast tumor on which that concept was based pathologically was, I believe, an epidermoid cancer that invaded the superior sulcus involving the spinal cord. Today, we no longer adhere to that concept but rather refer to the Pancoast syndrome. Many tumors do produce a Pancoast syndrome with pain identical to that caused by the original Pancoast tumor.

DR. CASTLEMAN: In Pancoast's original papers there were no pathological studies at all. His cases were all clinical cases. Later, when some of these cases were proved to be squamous-cell carcinoma, the question arose whether they might have arisen from a branchial-cleft remnant. Some physicians believe that a small group of these cases may have an extrapulmonary origin, perhaps from a bronchogenic rather than a branchogenic rest. Most of the tumors that produce a Pancoast syndrome are primary in the lung or metastatic from some other source.

REFERENCES

1. Miller, W. S. *The Lung*. Second edition. 222 pp. Springfield, Illinois: Thomas, 1947.
2. Herbut, P. A., and Watson, J. S. Tumor of thoracic inlet producing Pancoast syndrome: report of 17 cases and reviews of literature. *Arch. Path.* 42:88-103, 1946.

CASE 40522

PRESENTATION OF CASE

A thirty-two-year-old woman, Para 5, Gravida 5, was referred to the hospital because of foul-smelling vaginal discharge.

She had been hospitalized because of pneumonia seven years, a negative breast biopsy five years and two umbilical herniorrhaphies and an appendectomy two years previously. She had been asymptomatic until a normal delivery three months before admission. Five days after delivery she had severe chills and a thick mucopurulent vaginal discharge that continued for five weeks. Two weeks before admission vaginal bleeding required ten to twelve packs a day for two days. Seven days later a brownish vaginal discharge with an offensive odor appeared.

She had had a decrease in appetite for two months, an occasional sharp, stinging sensation in the left lower quadrant near the herniorrhaphy scar and occasional wheezing dyspnea previously diagnosed as bronchial asthma.

The temperature was 98.6°F., the pulse 90, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

Physical examination revealed an asthmatic, pale, ill woman with a tender liver edge 1 cm. below the right costal margin in the midclavicular line. There was diffuse abdominal tenderness that was greatest in the left lower quadrant. An umbilical herniorrhaphy scar was present, and there was a left indirect inguinal hernia. On vaginal examination a copious, foul, milky discharge and a large 7-cm. firm mass projecting through a dilated cervix were found. A suprapubic mass was also felt and was described as being tender.

The urine gave a + test for albumin; the sediment contained bacteria and 10 white cells per high-power field. There was no glycosuria. The serum nonprotein nitrogen was 15 mg., and the blood hemoglobin 13.8 gm. per 100 cc.

On the second hospital day an operation was performed.

Differential Diagnosis

Dr. Frank C. Wheelock, Jr.*: This woman's trouble apparently started after her fifth normal delivery, when she had a vaginal discharge and fever; ten weeks later she had some bleeding. This bleeding may well, of course, have been the first normal period after pregnancy, which is sometimes delayed. She may have taken estrogens as many women do nowadays to diminish the output of milk in the breast, and the bleeding may have been associated with that, but we have no indication that she had. Moreover, the bleeding stopped right away so it probably had more to do with the mass than with any hormonal situation. Tenderness developed in the left lower quadrant, but there is no recorded fever or increased white-cell count so that whatever the inflammatory process was it could not have been acute. On examination the physicians found a mass as well as the discharge of which she complained.

I think there are two main groups of lesions to consider: neoplastic diseases and conditions associated with the recent pregnancy. Of the neoplastic group those that occur within the uterus, whether it is normal or just after a delivery, include a cervical polyp. It is difficult to see how such a polyp would have been missed at delivery. It would have to have been of some size because it grew to 7 cm. only a few months after delivery. A cervical polyp, of course, is almost always benign. An endometrial polyp can grow to quite a large size. The largest one that I have seen measured about 7 cm.; it did not happen to protrude from the cervix. It is difficult to see how this patient could have had a very large endometrial polyp and a normal pregnancy. Endometrial polyps, of course, are occasionally a manifestation of carcinoma-in-situ or carcinoma of the endometrium. A large pedunculated fibroid or even a fibroid with sarcomatous degeneration could hang down from the interior of the uterus and be obvious on examination, but it is difficult to believe that either could occur with a normal pregnancy and delivery. There is no reason to think of a tumor of the cervix itself from the history, and a malignant tumor such as carcinoma of the cervix is almost out of the question.

Two neoplasms, which I might mention briefly and exclude, are hydatidiform mole and chorioepithelioma. Hydatidiform moles, of course, do not occur after normal deliveries. They are associated with blighted ova and miscarriages early in pregnancy. Chorioepitheliomas are extremely rare tumors, occurring about once in every 160,000 deliveries. Most of the chorioepitheliomas are benign, contrary to what the name usually connotes to most of us. Only 1 in about 6, according to Hertig,[1] turns out to be of the metastasizing kind that has such a universally bad outcome. The rest he divides into more or less benign types. In this patient there was little to suggest a tumor; she did not bleed consistently; the mass described sounds more like a pedunculated affair than an invasive tumor. No Aschheim–Zondek test was reported — with either hydatidiform mole or chorioncarcinomas the test would be positive in an unusually high dilution.

The second and more likely cause of the trouble was some condition complicating the delivery. It is difficult to believe that anything but the placenta could have been at fault. If a piece of placenta had been left behind at the time of the delivery, it could have formed a polyp and grown to this size. A placental polyp is made up of chorionic villi, decidua and fibrous tissue and can grow to a modest size. Certainly, any of these tumors, either the neoplastic ones or the placental polyps, could very easily have produced all these symptoms — the vaginal discharge, the bleeding and possibly the discomfort if there was an associated chronic infection of the pelvic organs. There certainly could have been some kind of sapremia, with a slight fever and not much increase in neutrophils, that would have allowed the patient to carry on normal activities. The symptoms do not help me to tell exactly what kind of tumor was present because any tumor in a uterus shortly after delivery could easily become sufficiently infected to cause these various symptoms. I should assume that the asthma had nothing to do with the present illness.

A foreign body is another possibility that one should always consider when there is an unusual discharge from any orifice or sinus, but it is difficult to see how any foreign body could conceivably have avoided falling out. There is little reason to suppose that the patient had a complication of a new pregnancy. She had hardly had time to become pregnant again, although a patient can certainly become pregnant even before one normal period occurs.

My final choice, then, is a placental polyp, with any of the other pedunculated tumors as second choice, but it is difficult for me to see how a large pedunculated tumor could have existed in a patient who had had a normal pregnancy such a short time before.

Clinical Diagnosis

?Inversion of uterus.
?Uterine fibroid.

Dr. Frank C. Wheelock, Jr.'s Diagnosis

Placental polyp.
?Pedunculated uterine tumor.

Anatomical Diagnosis

Prolapsed submucosal leiomyoma of uterus, with infarction.

Pathological Discussion

Dr. Austin L. Vickery: The operation performed was a hysterectomy. The gross examination of the uterus revealed a large, intra-uterine, freely

*Assistant in surgery, Massachusetts General Hospital.

movable, polypoid mass measuring 11 cm. in length and 6 cm. in diameter that was attached to the fundus by a stalk and protruded from the cervical os. There were areas of necrosis in the tumor that were thought to be attributable to infarction from torsion of the peduncle. The foul-smelling vaginal discharge was traceable to these necrotic zones. On cross section, the tumor presented a solid appearance except for some small cysts and the degenerated regions. Histologically, the picture was one of a leiomyoma. Submucosal leiomyomas in this location just beneath the endometrium comprise about 5 per cent of all uterine leiomyomas; however, they are more likely to produce symptoms than those occurring in any other portion of the uterine wall. Regarding the association of pregnancy and submucosal leiomyomas, Novak[2] refers to a series in which 80 per cent of patients with submucosal leiomyomas, which might be expected to offer the greatest obstacle to pregnancy, had had children. In this particular case the chances are that the tumor had been present for some time.

DR. BENJAMIN CASTLEMAN: Do you think it is possible that the fetus itself had pressed against this leiomyoma and caused the necrosis?

DR. VICKERY: I suppose that is possible. The patient was almost three months post partum before the foul-smelling vaginal discharge began that was most probably due to ischemia caused by a twisting of the "fibroid" peduncle; however, the earlier symptoms could have been related to that mechanism.

DR. JACOB C. LERMAN: This fibroid could have been a small one that started to grow with the stimulation of pregnancy. Many fibroids grow large during pregnancy.

REFERENCES

1. Hertig, A. T. Hydatidiform mole and chorionepithelioma. In *Progress in Gynecology*. Vol. 2. 821 pp. Edited by J. V. Meigs and S. H. Sturgis. New York: Grune and Stratton, 1950. Pp. 372-394.
2. Novak, E. *Gynecological and Obstetrical Pathology*. 595 pp. Philadelphia: Saunders, 1952.

ADDENDUM TO CASE 40342*

DR. BENJAMIN CASTLEMAN: After the spinal fusion local recurrence of the lesion developed. This eventually led to spinal-cord compression and paraplegia. Another biopsy at a decompression operation revealed malignant lymphoma microscopically:

> The tumor, which is composed of small round cells containing only a narrow rim of cytoplasm, resembles the frozen section noted at the original operation, but does not have the features of the lesion finally found in the transverse process and interpreted as eosinophilic granuloma. In the light of the present findings this reaction, with its eosinophilia and proliferation of histiocytes, must be considered as a reaction in the bone marrow to the invading tumor; it is unique in our experience with bone tumors. The present tumor belongs to the group of small-cell tumors of bone, and the cytologic appearance suggests that it is a malignant lymphoma.

X-ray therapy has produced some reduction in the size of the paravertebral mass, but the paraplegia is now permanent.

ANATOMICAL DIAGNOSIS (CASE 40342)

Malignant lymphoma of eleventh dorsal vertebra.

*Case Records of the Massachusetts General Hospital (Case 40342). *New Eng. J. Med.* 251:354-357, 1954.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Richard E. Alt, M.D.
Oliver Cope, M.D. — James M. Faulkner, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR
James F. Ballard, BOOK REVIEW EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. — Benjamin Castleman, M.D.
Robert M. Green, M.D. — J. Englebert Dunphy, M.D.
Dwight O'Hara, M.D. — Robert W. Buck, M.D.
Fletcher H. Colby, M.D. — Herrman L. Blumgart, M.D.
Robert L. Goodale, M.D. — Frank N. Allan, M.D.
Chester M. Jones, M.D. — Harvey A. Kelly, M.D.
Harvey R. Morrison, M.D. — Langdon Parsons, M.D.
Maxwell Finland, M.D. — Mark Ainser, M.D.
Vernon P. Williams, M.D. — Walter P. Lever, M.D.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (first-year interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

MANUSCRIPTS, including references or bibliography, should be typewritten double spaced and submitted as original copy. References should conform to the style of the *Quarterly Cumulative Index Medicus* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum.

ILLUSTRATIONS are reproduced as half tones and zinc etchings. Photographs must be distinct, and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal.

VIRAL ETIOLOGY OF ACUTE RESPIRATORY INFECTIONS

THE rapid progress that is being made in the field of viral diseases, thanks to the development and use of various tissue-culture methods, has been referred to on other occasions in these columns. The latest discoveries include a group of cytopathogenic agents, presumably viruses, isolated by Rowe and his co-workers[1] at the National Institutes of Health and the School of Hygiene and Public Health at Johns Hopkins University. These viruses were originally obtained from cultures of human adenoid tissues that were undergoing spontaneous degeneration and they were transmissible by serial passage in a variety of tissue-culture mediums, including those of HeLa cells and certain human embryonic tissues. One of these agents appeared to be similar to a cytopathogenic agent recovered by Hilleman and Werner[2] at the Army Medical Service Graduate School in tissue cultures of HeLa cells made from throat washings of a patient with primary atypical pneumonia, in whom specific neutralizing and complement-fixing antibodies for that agent developed; in other patients who were thought to have primary atypical pneumonia or undifferentiated acute respiratory diseases antibodies to that agent developed.

At the 1954 meeting of the Association of American Physicians, Dingle and his co-workers[3] reported a study designed to determine the relation of the Hilleman and Werner virus to certain clinical syndromes of acute respiratory disease. For their study they had several groups of serums that had been collected by the Commission on Acute Respiratory Diseases in human transmission experiments of various respiratory infections and also from many clinical cases diagnosed as "acute respiratory disease." They also studied a number of pools of Red Cross gamma globulin. They titrated the serums taken during the acute and convalescent phases of illnesses characterized clinically as primary atypical pneumonia, acute respiratory disease of recruits, mild common cold, severe common cold and bronchitis resembling atypical pneumonia. They were able to demonstrate a clear-cut rise in antibodies during convalescence only in patients with the clinical syndromes of acute respiratory disease and in those with bronchitis resembling atypical pneumonia, but not in patients with mild or severe common cold or with definite syndromes of primary atypical pneumonia. Likewise, in the serums from the subjects of their transmission experiments, a rise in antibody against the Hilleman–Werner agent was detected only in the recipients of material from donors who had "acute respiratory disease" or bronchitis.

The results obtained by Dingle and his associates were even more striking when they were analyzed for the presence or absence of antibody against the Hilleman–Werner agent in the acute-phase serum of the recipients of the materials in the study on acute re-

spiratory disease. Fifteen of the 18 volunteers who had clinical manifestations of the disease had no detectable antibody in their preinoculation serums and had rises in antibody titer. On the other hand, 5 of the 6 volunteers who failed to manifest symptoms had appreciable titers of antibodies in their acute-phase serums. These findings suggested that the presence of antibodies may afford protection against the acute respiratory disease produced by this and similar viruses.

Additional studies carried out by Dingle and his associates included titrations of serums from clinical cases of acute respiratory diseases in several military installations. The results suggested that the infection called "acute respiratory disease" at two of the installations appeared to be caused by the Hilleman–Werner virus or an immunologically related one, whereas the serums of all but 1 patient with the same diagnosis at another installation failed to show such antibodies. These findings suggested that more than one immunologically distinct virus was responsible for this type of respiratory disease.

The studies of samples of concentrated gamma globulin prepared from large pools of blood obtained by the Red Cross also demonstrated neutralizing antibodies. Almost all the specimens contained antibodies in high titer. These data suggested that specific antibodies existed in a relatively large proportion of the civilian population and that a disease due to this or related viruses must exist among civilians as well as in military populations.

The original report on the "adenoid degenerating agent" indicated that 13 isolations of the new agent had been made but cited no evidence of their relation to human disease. Elsewhere in this issue of the *Journal*, Huebner and his co-workers have reviewed their studies and brought them more nearly up to date. They have uncovered 143 strains and now designate them as adenoidal-pharyngeal-conjunctival agents. They have also succeeded in segregating 6 immunologic types, all of which grow readily, with similar and unique cytopathogenic effects in human epithelial and HeLa cells. They are resistant to ether and antibiotics. They are not pathogenic for common laboratory animals but cause type-specific and a lesser amount of heterotypic neutralizing antibodies.

These authors also summarized their epidemiologic studies, which indicate that viruses of all 6 types produce frequent infections in man, beginning at an early age, many persons suffering infections with several types by the time they reach adolescence. There is more convincing evidence that Types 3 and 4, in particular, are causes of specific respiratory illness. The prototype for the latter was the agent reported by Hilleman and Werner as being responsible for some cases of acute respiratory disease and primary atypical pneumonia in military personnel.

A companion paper by the workers at the National Institutes of Health, published in this issue, presents evidence that Type 3 of the adenoidal-pharyngeal-conjunctival viruses was responsible for a small outbreak of acute respiratory infection with fairly distinctive clinical features. These include rhinitis, pharyngitis, fever, cervical or submandibular lymphadenopathy, conjunctival inflammation and liver tenderness. Some of the cases, as described by the authors, had many features that make them hard to distinguish from the common cold; others were similar to those described by Dingle and his co-workers as "acute respiratory disease." Another recent report by Dingle's group[4] indicates that the Hilleman–Werner virus has produced few infections in Cleveland recently. Serums collected from children in 1954 had no neutralizing antibodies for this virus, whereas such antibodies were demonstrated in the serums of mothers (17 per cent) and fathers (53.7 per cent). On the other hand the authors presented evidence that a strain similar to adenoidal-pharyngeal-conjunctival virus Type 3 has recently been associated with syndromes that they classify as "acute respiratory disease" and "nonstreptococcal pharyngitis."

Thus, the intensive activities in the search for the cause of the common cold and similar acute respiratory diseases are beginning to bear fruit. The reports from the National Institutes of Health are also interesting, however, because they provide an example of a group of viruses discovered and propagated without any definitely known relation to disease, and subsequently, as a result of intensive epidemiologic studies, a clinical syndrome is encountered that is demonstrated to be related to one of the viruses previously discovered. There now appear to be numerous viruses in the same group, as there also seem to be within the group of Coxsackie viruses, whose etiologic relation to specific diseases has not yet been proved.

References

1. Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., and Ward, T. G. Isolation of cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. *Proc. Soc. Exper. Biol. & Med.* 84:570-573, 1953.
2. Hilleman, M. R., and Werner, J. H. Recovery of new agent from patients with acute respiratory illness. *Proc. Soc. Exper. Biol. & Med.* 85:183-188, 1954.
3. Dingle, J. H., Ginsberg, H. S., Badger, G. F., Jordan, W. S., Jr., and Katz, S. Evidence of specific etiology of "acute respiratory disease (ARD)." *Tr. A. Am. Physicians* 67:149-155, 1954.
4. Jordan, W. S., Jr., Badger, G. F., Dingle, J. H., Ginsberg, H. S., and Katz, S. Serologic epidemiology of respiratory agents isolated in HeLa cell cultures. *J. Lab. & Clin. Med.* 44:816, 1954.

AMERICAN-JEWISH TERCENTENARY

THE Jews of America, and with them the country at large, celebrate this year the three hundredth anniversary of Jewish settlement on the continent. The observance, which began on September 12, 1954, and will continue until May 29, 1955, marks the migration, in 1654, of 23 Jewish refugees from Brazil to the colony, then Dutch, of New Amsterdam. From this original small nucleus the present American-Jewish citizenry of over 5,000,000 persons has grown, making,

as it developed, its series of notable contributions to every phase of American life and furnishing outstanding leadership in many of them.

The Tercentenary Committee has for associate chairmen a number of the country's leading Jewish citizens; the theme of the celebration is "Man's Opportunities and Responsibilities under Freedom." Both American and Jewish aspects of the observance are brought out by such a theme, and the universal rather than the nationalistic traditions of Judaism are thus stressed. The Tercentenary not only features the integration of the Jewish people into the life of the country, but also the contributions that they have made to its culture.

As parts of the diversified celebration historical exhibits have been collected, a series of significant plays

has been arranged, and a new symphony has been written. Jewish Book Month was set apart, from November 19 to December 19, and a 20-volume History of the Jews has been planned, to be written by 30 scholars in Israel and 50 in the United States — an undertaking that reminds one of the labors of the Septuagint.

In no branch of learning and of service have Jews been more prominent than in medicine, in honor of which the Boston Medical Library has prepared an exhibit to portray this side of Jewish culture. The exhibit, containing a large collection of Jewish writings in Hebrew and in Latin, dating from the time of the School of Salerno until the present, will be on view until May 1, 1955.

CHEMUNG COUNTY TAKES A STAND

THE Chemung County Medical Association of New York State, according to an Associated Press dispatch, announced in November that it would not support the national fund-raising drive of the Muscular Dystrophy Association. This action was taken in view of the facts that there were then only 3 known cases of muscular dystrophy in the county and these were cared for by private parties; that in the previous year $8600 was raised in the county for the Muscular Dystrophy Association and that only $70 came back, in the form of a wheel chair; and that in the same year $4,000,000 had been raised nationally, of which only $1,000,000 had been spent for research.

In rebuttal, the chairman of the national fund of the Association stated that $3,900,000 and not $4,000,000 had been raised, and that $2,000,000 had been spent on research. He further announced that 200,000 children now suffer from the disease and that "every cent is needed to fight this child killer."

In view of another United Community Services campaign having failed to attain its goal in Greater Boston, a failure attributed at least in part to the multiplicity of competing fund-raising agencies, actions such as that of the Chemung County Association should be viewed with interest. In fact, the question may be raised whether very many of the relatively minor appeals that continue to maintain an independent status deserve as much support as they seem able to enlist.

ANTIBIOTIC MEDICINE

THE newest addition to the great world family of medical periodicals, now estimated at over 10,000, is scheduled for delivery some time in January, 1955. *Antibiotic Medicine*, announced as a new companion journal to *Antibiotics and Chemotherapy*, will be, according to MD Publications, Incorporated, its creators, exclusively devoted to clinical studies and practice of antibiotic therapy.

The editor in chief of *Antibiotic Medicine* is Henry Welch, Ph.D., and the associate editor Félix Martí-Ibáñez, M.D. The board of 9 international and 25 national editors consists of well known authorities in the broad field of infectious disease. No less than 7 members of this illustrious group are Nobel Prize laureates.

The first issue of the new journal will contain editorials by Charles L. Rein, M.D., associate professor of clinical dermatology and syphilology, New York University Post Graduate Medical School; Arthur M. Walker, M.D., secretary, Streptomycin Committee, Veterans Administration; Maxwell Finland, M.D., associate professor of medicine, Harvard Medical School; and Harry F. Dowling, M.D., professor of medicine and head of department, University of Illinois College of Medicine. In addition a number of original articles will appear on various aspects of chemotherapy, with abstracts in Spanish.

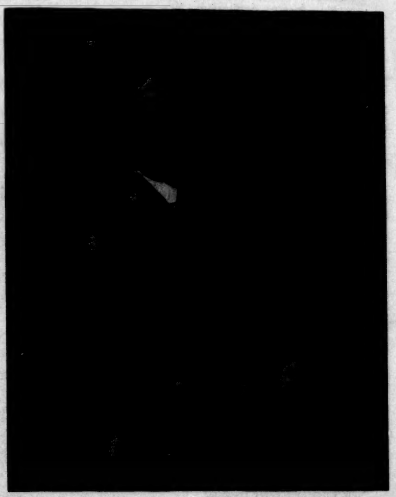
The whole family of a physician in New York City, together with their invited guests, were recently thrown into the greatest state of excitement at the tea-table in consequence of one after another of them being taken with nausea and vomiting. It appears that the cook, instead of cream of tartar to make bread with, had made use of tartar emetic from the doctor's office.

Boston M. & S. J., *Jan. 3, 1855*

MASSACHUSETTS
MEDICAL SOCIETY

TIMOTHY LEARY
1870-1954

Dr. Timothy Leary died in Jamaica Plain, Massachusetts, on November 16, 1954, at the age of eighty-four. He was born in Waltham, Massachusetts, in 1870. He attended Harvard College, graduating in 1893, and received his medical degree from Harvard



Medical School in 1895. After graduation, he became the first resident assistant pathologist at the Boston City Hospital and served in this capacity for two years. In 1897 he was appointed assistant professor of pathology and bacteriology at Tufts College Medical School. He served in the Spanish-American War, first as Commanding Officer of the United States Army Hospital in Ponce, Puerto Rico, and later as pathologist to the Yellow Fever Board in Santiago, Cuba. In 1900 he became professor of pathology and bacteriology at Tufts College Medical School; he held this position until 1929, when he became emeritus professor. At this time he established the Leary Laboratory, which has been of great service to small hospitals as well as large numbers of physicians. In 1908 he was appointed associate medical examiner for Suffolk County, Massachusetts, and, in 1910, medical examiner. He retired from this position in 1950. In 1939 he was made lecturer in pathology at Harvard Medical School.

Dr. Leary was one of the original trustees of the Forsyth Dental Infirmary for Children in Boston, in which he was greatly interested, devoting much time and energy to its development. He was a member of numerous medical societies and was a past president of the Massachusetts Medico-Legal Society, the Massachusetts Society of Examining Physicians and the Boston Pathological Society.

In 1907 he received an honorary degree of Master of Arts from Tufts College. He received the Silver Medal for Original Work of the American Medical Association in 1934. He was awarded the Charles V. Chapin Gold Medal by the Rhode Island Medical Society in 1942. In 1952 he was awarded the Leonard Wood Medal by the Boston City Hospital House Officers' Association.

During his service as medical examiner, he performed some 15,000 autopsies. He took advantage of this large amount of material to make numerous scientific observations on the early stages and natural course of disease as well as the results of trauma of various types. Such observations bore fruit in his studies on subdural hemorrhages, rheumatic fever, coronary-artery disease and atherosclerosis.

In his medicolegal work Dr. Leary showed great attention to detail and acuity in detecting crimes where none had been suspected, and conversely saved many innocent persons against whom the evidence seemed conclusive. He was an enthusiastic advocate of the Massachusetts medicolegal system as contrasted to the coroner system used so widely elsewhere. To extend the Massachusetts system and to train men properly for this field was one of his ideals.

During his service as medical examiner his office and laboratory were in the Boston City Hospital, but he had no official connection with it. However, he was intensely loyal to the Hospital and, wherever possible, protected its interests. He had a thorough understanding of the frailties of human nature and a profound pity for the unfortunate. These feelings were expressed practically by his shielding such persons as far as possible from unnecessary scandal.

After his retirement from Tufts in 1929, Dr. Leary had an opportunity to devote himself to investigative work, and his publications during the next two decades demonstrated his ability in this branch of medicine.

Among the first in this series was the description of the early lesions of the heart in rheumatic fever. Subsequently, impressed by the frequency of subdural hemorrhage as a cause of death, he carried out a study of the subdural space and hemorrhages. As a result, he was able to point out and recommend certain surgical procedures that have resulted in the saving of numerous lives.

Struck by the frequency of coronary-artery disease as a cause of death, especially in the younger age groups, Dr. Leary published a series of papers on its genesis, especially atherosclerosis. As a corollary he began his studies on atherosclerosis and its relation to cholesterol, both from an experimental and from a morphologic standpoint. For the remainder of his life, his work was chiefly concerned with cholesterol and its role in the production of human disease, particularly atherosclerosis, and later the relation of cholesterol to human neoplasms, especially those of the kidney and prostate.

Dr. Leary was keenly interested in the problem of alcoholism on account of the numerous victims that passed through his hands. He bewailed the availability in Massachusetts of ethyl alcohol and the inferior grade of many of the brands of whisky. He wrote and spoke many times on this subject.

Among his other interests besides scientific work was early American history. He firmly intended to write a biography of Benjamin Church, but lack of time and failing health made this impossible. He was interested in art and had a notable collection of drawings, etchings and old books. Gardening also gave him great pleasure, and he took great pride in his flower garden, in which he worked assiduously in his younger days.

Dr. Leary possessed boundless energy and enthusiasm. He reveled in his work and seemed tireless. He was kindness itself to the younger members of the laboratory staff and always invited them up to his autopsy room to demonstrate anything of special interest. He was a brilliant writer, with the ability to express himself clearly and forcibly.

As a rule he was calm and good natured, but on occasion he could display a very active temper. The usual cause for such pyrotechnics was when any of the clinical services broke one of his ironclad rules regarding medicolegal autopsies. On such occasions, the hapless intern was informed of his transgression in no uncertain terms. He detested hypocrites and poseurs of any sort, as many an opponent in the courtroom learned to his sorrow.

Dr. Leary is survived by his wife, Dr. Olga Cushing Leary, and by two daughters, Dr. Olga Leary and Dr. Deborah Cushing Leary.

There hangs in his house an illuminated scroll, whose inscription well expresses the feelings of his friends and associates:

TIMOTHY LEARY, M.D.

Pathologist, Teacher, Medical Examiner in Suffolk County from 1908 to 1950, whose career and unswerving devotion to duty has always been an inspiration and example to his pupils and associates — this scroll is presented by his fellow members of the Massachusetts Medico-Legal Society, October 18, 1950.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JANUARY 6

THURSDAY, JANUARY 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Thoracic Conference. The Use of Hypothermia in Cardiac Surgery. Dr. William Bernhard. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
12:00 m.–1:00 p.m. Staff Conference. A Long Range Study of Neurologic Sequelae Following Spinal Anesthesia. Dr. Leroy D. Vandam. Stearns Auditorium, New England Center Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:30–5:30 p.m. Medical Treatment of Gastric Lesions — Indications for Surgical Intervention. Dr. John F. Fagan. Auditorium, Nurses' Home, Cambridge City Hospital.

FRIDAY, JANUARY 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30 a.m. Blood Typing Including Rh (Movie). Conference Room, Salem Hospital, 81 Highland Avenue, Salem.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JANUARY 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30 a.m.–12:00 m. Middlesex South District Medical Society. Postgraduate Course. Office Gynecology and Endocrinology. Drs. George V. Smith and Somera H. Sturgis. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, JANUARY 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. Observer Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Pharmacology of Ether — Divinyl Ether. Dr. Leroy Vandam. Surgical Conference Room, Peter Bent Brigham Hospital.

(Concluded on page xiv)